ABSTRACTS OF WORLD MEDICINE

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Pathology

1240. **Rapid Colorimetric Micro-method for Estimating Glucose in Blood and C.S.F. Using Glucose Oxidase**
J. E. MIDDLETON and W. J. GRIFFITHS. *British Medical Journal* [*Brit. med. J.*] **2**, 1525–1527, Dec. 28, 1957. 2 figs., 13 refs.

Glucose oxidase is an enzyme which specifically oxidizes β-glucose to gluconic acid, with formation of hydrogen peroxide. The authors describe a special reagent containing glucose oxidase, phosphate buffer, peroxidase, and *o*-tolidine for use in a rapid colorimetric micro-method for the estimation of glucose in the blood and cerebrospinal fluid. To 4 ml. of the reagent is added 0·2 ml. of a clear Somogyi-type protein-free blood filtrate. After mixing this is allowed to stand at room temperature for 10 minutes when the colour is read in a photo-electric absorptiometer at 680 mμ against a blank of buffered enzyme–dye solution. Various glucose standards are similarly treated.

This enzyme method has been compared with that of Asatoor and King (*Biochem. J.*, 1954, **56**, xliv) in 64 parallel estimations; the coefficient of correlation between the two methods was 0·995. MacLean's method gives higher values, since it includes reducing substances other than glucose. The authors suggest that the accuracy and convenience of the method described are such that it can replace the usual copper-reducing methods with great economy in time and materials. They add that the method showed the fasting blood glucose level in normal subjects to range from 50 to 90 mg. per 100 ml., rising to approximately 160 mg. per 100 ml. after the ingestion of glucose.

C. L. Cope

1241. **A Simple Discriminatory Test for Upper Gastro-intestinal Hemorrhage**
W. V. MCDERMOTT. *New England Journal of Medicine* [*New Engl. J. Med.*] **257**, 1161–1164, Dec. 12, 1957. 3 figs., 5 refs.

When haemorrhage occurs into the gastro-intestinal tract excess ammonia is released into the portal circulation by the action of intestinal flora on the nitrogenous "meal". This ammonia is normally detoxicated in the liver, but in the presence of a portal–systemic collateral system, as in hepatic cirrhosis, it will pass directly into the peripheral blood. It is suggested that since oesophageal varices—a manifestation of this collateral system—are an important cause of gastro-intestinal haemorrhage, estimation of the blood ammonia level, which demonstrates this shunt, may be a valuable aid in the differential diagnosis. Quantitative estimations of the blood ammonia level call for highly-skilled personnel; the author, working at Harvard Medical School, has therefore devised a relatively simple qualitative test, using a Conway micro-diffusion chamber, which, he claims, can be employed by personnel who are unfamiliar with the quantitative technique. [For details the original paper should be consulted.] With this technique, which will detect ammonia levels over 120 μg. per 100 ml. (normal range, 40 to 60 μg. per 100 ml.), the author obtained a high degree of diagnostic accuracy, with only one false positive and one false negative result in 100 cases of gastro-intestinal haemorrhage.

M. Sandler

EXPERIMENTAL PATHOLOGY

1242. **Experimental Anemic Infarction of the Lung. The Morphologic Evolution of True Infarcts of the Lung Produced with a Halogenated Hydrocarbon**
M. F. STANTON and R. STOUFER. *American Journal of Pathology* [*Amer. J. Path.*] **33**, 1099–1119, Nov.–Dec., 1957. 14 figs., 34 refs.

During an investigation of the toxicity of halogenated hydrocarbons it was found that a single sublethal intravenous injection of certain of these compounds produced multiple anaemic infarcts in the lungs of rabbits and dogs.

The sequence of changes was identical with that observed following obstruction to an end-artery. The early and late morphological changes are described in detail. No attempt was made to clarify the pathogenic mechanisms involved, although it was noted that blood coagulation was unaltered by these substances. Since infarction was in progress before thrombi developed in the lung vessels, it is considered that the lesion was produced by direct chemical action on the capillary bed.

J. B. Cavanagh

1243. **The Effects of High Blood Cholesterol on the Pulmonary Arterial Changes Produced in Rabbits by the Injection of Blood Clot**
R. H. HEPTINSTALL. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **38**, 438–445, Aug., 1957. 12 figs., 14 refs.

In the experiments on rabbits here described from St. Mary's Hospital, London, 4 of the animals were fed on unlimited amounts of cholesterol-impregnated food and served as donors of cholesterol-rich blood from which

emboli for injection into the other rabbits were prepared. Blood was taken from a marginal ear vein and allowed to clot in the pipette; the clot was then suspended in saline and injected into the marginal ear veins of the recipient animals; the suspensions contained a mean of 1,900±700 mg. of cholesterol per 100 ml.

The animals were in four groups. (1) The 24 rabbits in this group were fed on hay and water and after the injection of clot on each of 3 successive days were killed at intervals of between 3 and 21 days. Those killed within 7 days of the first injection showed acute arteritis in the pulmonary arteries of all sizes, involving the intima and adventitia and in some cases also the media; 9 out of 12 of these animals showed organizing emboli, but only 2 out of the 12 showed anisotropic lipid in the emboli and this was contained in small numbers of foam cells. In rabbits killed after 8 to 14 days the arteritis was less severe and the emboli were less cellular, were devoid of fibrin, and contained young collagen; cholesterol was present in only one out of 7 animals. In those killed at 21 days there was no longer any evidence of arteritis or of organizing emboli. Most of the animals showed fibro-elastic thickening of the intima, especially at points where the thickness of the vessel wall became reduced to give rise to thinner-walled branches. The internal elastic lamina was often reduplicated in the animals examined at the longer intervals after injection. (2) The 20 rabbits in this group were fed on a diet containing 0·6 g. of cholesterol daily for 17 days and were injected as in Group 1 after the first 10 days. A similar picture of arteritis and embolism was produced, but mononuclear cells containing anisotropic lipid were found frequently in the lesions, and foam cells were found diffusely in the arterial intima, either in the form of polypoid masses projecting into the lumen or arranged circumferentially. (3) This control group consisted of 10 rabbits which were fed on the same diet as Group 1 but received no injections. They showed no evidence of arteritis, embolism, or lipid deposition, although mild to moderate degrees of fibro-elastic thickening were present in 8 of the animals, especially where the vessel wall became thinned at the origin of its branches. (4) The second control group, also of 10 rabbits, were fed on the same cholesterol diet as Group 2, but were not injected. They showed mild to moderate degrees of fibro-elastic intimal thickening in all but one animal and cholesterol was either absent or present in only small amounts in the intima.

The striking feature of these experiments was the large amount of cholesterol-containing macrophages in the intima in animals in Group 2, in contrast with their paucity in those in Group 4. The number of foam cells in Group 2 after approximately 3 weeks of cholesterol feeding was comparable with that in uninjected animals given 0·5 to 0·6 g. of cholesterol daily for 10 weeks. In the animals in Groups 2 and 4 the serum total cholesterol levels varied from 450 to 2,400 mg. per 100 ml. during the period of cholesterol feeding. It is thought that the increased deposition of cholesterol in the intima was probably due to the initial arteritis, the rise in pulmonary blood pressure resulting from embolization being considered too transient to account for it; moreover, the distribution to the deposits was not strictly related to the distribution of the emboli. However, the findings were in keeping with the concept of injury to the arterial wall as an explanation of the localization of atheromatous foci.

Robert de Mowbray

1244. **Thromboembolism and Experimental Systemic Arteriosclerosis**

E. R. Rabin, W. A. Thomas, Kyu Taik Lee, N. Konikov, and R. F. Scott. *A.M.A. Archives of Pathology* [*A.M.A. Arch. Path.*] **64**, 75–81, July, 1957. 11 figs., 8 refs.

Previous workers have experimentally produced arteriosclerosis of the small pulmonary arteries. In this paper from Washington University School of Medicine, St. Louis, Missouri, the authors describe a method for the experimental production of arteriosclerosis of the systemic arteries of rabbits by the repeated injection of blood clot into the general circulation. Blood obtained from healthy animals by cardiac puncture was rapidly beaten to produce a clot consisting mainly of fibrin. A saline suspension of the clot was prepared and coloured with indian ink; either 1 ml. was injected into the heart of the recipient animal on one to 7 occasions over 2 to 57 days or the clot formed from 3 ml. of blood was injected into the central artery of the ear on a single occasion.

The animals receiving intracardiac injections developed no gross lesions in the aorta or in the other large arteries, but 16 developed myocardial infarcts and 15 developed renal infarcts; some of these infarcts were recent, while others were organized. Many of the myocardial infarcts contained small collections of fat and some were calcified. The arterial lesions produced were of two types: (1) organizing thrombus partially or completely occluding the lumen and often showing multiple recanalization; or (2) fibrous intimal plaques containing no fat, calcium, or haemosiderin. In both types of lesion the internal elastic lamina was usually intact. Similar arterial lesions were produced in the arteries of the ear after direct intra-arterial injection. It was noted that only a minority of the fragments of blood clot injected produced arterial lesions, direct observation through a transparent ear-chamber of the injected suspension marked with indian ink showing that most of the clots disintegrated rapidly and were not incorporated into the vessel walls. Identical lesions were produced by intracardiac injections of blood-clot suspensions not marked with ink. In control groups no lesions developed in animals injected with indian ink alone, in animals bled from the heart but not given injections of blood clot, or in animals given intra-arterial injections of saline under high pressure.

In a further experiment 13 rabbits were given supplements of 2 g. of cholesterol in the daily diet. Those receiving the cholesterol but no injections of blood-clot suspension developed subendothelial plaques of fat-containing mononuclear cells and extracellular fat, whereas those given the cholesterol and in addition intracardiac or intra-arterial injections of blood clot developed the arterial lesions characteristic of both these procedures. In the animals receiving cholesterol the myo-

cardial infarcts and some of the thrombo-embolic arterial lesions contained more fat than did similar lesions in the rabbits not given cholesterol.

The authors suggest that the method described should be of value in the further investigation of the relationship between lipid and thrombotic factors in arterial disease.

Robert de Mowbray

1245. **Experimental Evidence for an Allergic Basis for Granuloma Formation in Man**

W. B. SHELLEY and H. J. HURLEY. *Nature* [*Nature (Lond.)*] **180**, 1060–1061, Nov. 16, 1957. 7 refs.

In view of reports of axillary granuloma occurring in association with the use of zirconium-containing deodorants, an experiment was carried out on 10 normal healthy male volunteers at the Department of Dermatology of the University of Pennsylvania, Philadelphia. Each of the 10 subjects was given 4 injections of 0·02 ml. of a 1% solution of sodium zirconium lactate into the skin and 4 injections into the subcutaneous tissue of the upper arm. Small papules developed at the sites of the intradermal injection, but the sites of subcutaneous injection could not be identified clinically. However, at the end of 6 months one of the subjects developed an enlarging nodular mass at each of the 8 sites of injection. Examination of biopsy specimens showed that there was replacement of the dermis and subcutaneous tissue with nests of epithelioid cells, with minimal round-cell infiltration.

Although none of the other subjects tested showed any clinical or histological response to intradermal injections of sodium zirconium lactate, the subject described above was now found to be sensitive to this substance in a dilution of 10^{-6}, and the papules produced by such injections also showed perivascular infiltration with epithelioid cells. Further, on examination of 6 patients who had developed axillary granuloma following the clinical use of deodorants containing zirconium it was possible to demonstrate in every case delayed local granuloma formation at the site of injection of 0·02 ml. of a 10^{-3} dilution of sodium zirconium lactate. These results indicate that in man there may develop a delayed granulomatous epithelioid-cell response as a result of a specific, acquired, generalized hypersensitivity to a simple metallic element.

H. A. Sissons

1246. **The Influence of Streptococcal Toxin on the Course of Canine Experimental Nephrosis**

K. G. WAKIM and B. F. MCKENZIE. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **50**, 410–416, Sept., 1957. 3 figs., 11 refs.

In a previous paper from the Mayo Foundation (*J. Lab. clin. Med.*, 1956, **48**, 866) the authors described the production of experimental nephrosis in dogs by the intravenous injection of serum from rabbits sensitized to dog kidney, the disease produced closely resembling the nephrotic syndrome as it occurs in man. Since the latter is often associated with a history of septic sore throat, the authors have investigated the effect of the administration of streptococcal toxin on the course of the experimental disease, the methods used being similar to those reported in the earlier paper.

A number [not specified] of healthy young dogs were divided into 3 equal groups, the first being given rabbit nephrotoxic serum, the second a streptococcal culture filtrate, and the third a mixture of nephrotoxic serum and the streptococcal culture filtrate. The total dose of each when given separately was 4·4 ml. per kg. body weight divided into 9 intravenous injections administered over a period of 3 days. The third group received the same total dosage of nephrotoxic serum, 1 ml. of culture filtrate being added to each of the 9 doses. Blood and 24-hour urine samples were obtained daily during the first week and then 2 or 3 times a week for a total of more than 40 days after the injections, the total protein content of blood and urine being determined, the electrophoretic pattern of the serum proteins studied, and the blood urea and serum total cholesterol levels estimated.

The administration of nephrotoxic serum alone caused severe hypoproteinaemia, with reduction of the serum albumin and α_1- and γ-globulin levels, while some increase in the serum α_2- and β-globulin levels occurred, starting on the day after the first injection, reaching a peak about 2 days after the last injection, and persisting for about 3 weeks. The serum cholesterol and blood urea concentrations rose consistently soon after the course of injections was completed; proteinuria was most marked at this time, but had disappeared by the 20th day. The effects of streptococcal toxin given alone were similar, but were much milder and of shorter duration. (The authors intend to investigate the effects of larger doses of streptococcal toxin in a future study.)

The combined administration of nephrotoxic serum and streptococcal toxin produced effects very much like those of nephrotoxic serum alone, but the proteinuria was more prolonged (persisting for more than 40 days), the serum cholesterol and blood urea levels rose slightly higher, and the reduction in the serum γ-globulin content was greater. The authors regard this last finding as "a basic explanation for the susceptibility to infection encountered in nephrotic states".

I. Berkinshaw-Smith

HAEMATOLOGY

1247. **The Use of Radioisotopes in Diagnostic Hematologic Procedures. III. Simultaneous Cr^{51} and Fe^{59} Studies**

T. G. MITCHELL, R. P. SPENCER, and E. R. KING. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **28**, 461–468, Nov., 1957. 4 figs., 7 refs.

The authors describe the techniques developed at the National Naval Medical Center, Bethesda, Maryland, for the simultaneous use of radioactive iron (^{59}Fe) for estimating the turnover of plasma iron and its utilization by the erythrocytes and of radioactive chromium (^{51}Cr) for determining the survival time of erythrocytes and the blood volume. This has been made possible by the development of gamma-ray spectrometry, which enables the gamma rays emitted by the two isotopes to be distinguished and counted separately on the basis of differences in their energy. [For details the original

paper should be consulted.] The results of investigations carried out by this method on one normal subject and 6 patients with a variety of blood diseases are given.

Janet Vaughan

1248. **Thrombosis and Factor VII Activity**

L. POLLER. *Journal of Clinical Pathology* [*J. clin. Path.*] **10**, 348–350, Nov., 1957. 3 figs., 18 refs.

The author, using a heparin-sensitized method, has already shown that, statistically, the coagulation time of the blood is significantly shortened 48 hours after a thrombo-embolic episode, and has suggested that increased resistance to heparin may be related to the ability to produce thromboplastin in the plasma of such patients. In the present paper he describes an investigation of various aspects of thromboplastin production in two groups of patients at the Royal Infirmary, Liverpool. The first group consisted of 20 patients seen within 48 hours of clinical onset of thrombosis—coronary thrombosis in 18 and thrombophlebitis in 2. The second or control group consisted of 20 hospital patients without clinical evidence of thrombosis.

The most striking finding was a high level of Factor-VII activity in the plasma of patients in the first group compared with paired controls, and this finding, the author suggests, provides a firm basis for the administration of drugs of the coumarin group in the treatment of thrombosis. Another significant finding was a shortening of the heparin plasma clotting time in the patients with thrombosis. An increase in thromboplastin generation and a raised serum cholesterol level were less constant findings. No significant differences were found between the two groups in the results of the Quick one-stage prothrombin determination and the plasma Factor-V levels.

A. W. H. Foxell

1249. **The Distribution of Blood-group Substances in Human Gastric and Duodenal Mucosa**

L. E. GLYNN, E. J. HOLBOROW, and G. D. JOHNSON. *Lancet* [*Lancet*] **2**, 1083–1088, Nov. 30, 1957. 24 figs., 10 refs.

The authors report the results of an investigation carried out at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, by the fluorescent-antibody technique of Coons into the distribution of the blood-group substances A, Le^a, and H in the mucosa of fresh human gastric and duodenal tissue obtained at partial gastrectomy from 8 patients with gastric and 8 with duodenal ulcer, of whom 7 were of Blood Group A, one of Group B, and 8 of Group O.

Blood-group specific substances were found to be distributed in the various cells of the gastric and duodenal mucosa according to clearly defined patterns, which differed in the body of the stomach, the pylorus, and the duodenum. These patterns were independent of the secretor or non-secretor phenomenon, which appeared merely to determine one of the blood-group specificities present only in the superficial zone of the mucosa. In the deeper zone the specificity of the blood-group substance was in part determined by the ABO group of the individual and was independent of the secretor status, but in both the superficial and deep zones a third and variable factor, that is, the presence or absence of H substance, also affected the total pattern. Thus in the body of the stomach blood-group substance A was present in water-soluble form in very large amounts in the epithelium of the superficial zone of secretors of substance A, while in the deeper zone of both secretors and non-secretors of substance A the parietal cells contained large amounts of alcohol-soluble blood-group substance, but the zymogenic cells contained no blood-group substance. In the pyloric region of the stomach water-soluble blood-group substance was found in both the superficial and deep zones and was present in all the epithelial cells of the foveolae and pyloric glands; no alcohol-soluble substance was detected in this region. In the mucosa of the first part of the duodenum the blood-group substance, though present in both the superficial and deep zones, was chiefly found in the goblet cells and spread from these to cover the surface. The staining of the cells of Brunner's glands closely resembled that of the convoluted pyloric glands.

In the superficial mucosal zone of all three regions the specificity of staining was related to the secretor phenomenon, Le^a substance being present in A and AB non-secretors instead of A substance. In individuals of both Groups O and A the superficial gastric mucosa of both secretors and non-secretors stained brilliantly with anti-H conjugate, but the deeper zone of the body of the stomach was not stained, although those of the pyloric and duodenal regions did sometimes stain. No obvious features distinguishing cases of gastric ulcer from those of duodenal ulcer were discovered.

A. Ackroyd

1250. **Cause of Anomalous Results in the Erythrocyte Sedimentation Rate Using Wintrobe's Method**

F. T. SHANNON and E. G. L. BYWATERS. *British Medical Journal* [*Brit. med. J.*] **2**, 1405–1409, Dec. 14, 1957. 9 figs., 15 refs.

For the past 5 years the erythrocyte sedimentation rate (E.S.R.) of all in-patients at the Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, has been measured every week by both the Westergren and the Wintrobe methods, the total number of duplicate readings thus obtained being approximately 19,000. In order to study the incidence and causes of the anomalously low results sometimes obtained by the Wintrobe method in the presence of a very active disease process the authors have analysed the 2,540 pairs of readings from 100 patients selected at random. This group was mainly composed of children and young adults, of whom 40 had rheumatoid arthritis, 47 rheumatic fever or chorea, and the remainder other forms of collagen disease. The results were regarded as discordant if the Wintrobe E.S.R. was less than 20 mm. at a time when the Westergren rate was 50 mm. or more in one hour. In such cases the Westergren rate gave without exception the more accurate reflection of the clinical state. Anomalous readings were obtained by the Wintrobe method on at least one occasion in 26 out of the 100 cases and constituted 4·6% of the 2,540 readings. On 23% of the 498 occasions on which

the Westergren reading was over 50 mm. in one hour the results were discordant, and in this group of cases the mean packed cell volume (P.C.V.) was 40·6%; in the remaining 77% of cases the P.C.V. was 36·5%, the difference being highly significant.

Experiments were then carried out to determine how far the plasma viscosity, the P.C.V., and the internal diameter of the sedimentation tube were concerned in the causation of anomalous results by the Wintrobe method. Plasma viscosity was measured in a modified Ostwald capillary viscosimeter and expressed in terms of its relation to the viscosity of distilled water as indicated by its rate of flow at 37° C. It was found that as the relative plasma viscosity increased beyond 1·8 the mean Westergren reading rose steadily, whereas the Wintrobe reading increased more slowly to a maximum at a viscosity of 2·1 and thereafter fell again to the level attained at a viscosity of 1·9 to 2. The effect of increasing plasma viscosity on the Wintrobe reading was essentially the same whatever the P.C.V. of the blood. In the lower ranges of viscosity values the Wintrobe readings for blood with a P.C.V. below 39% were closer to the Westergren readings than those for blood with a higher P.C.V., but there was always a fall in the Wintrobe rate when the plasma viscosity rose above 2·1 or 2·2. The Westergren readings at different levels of viscosity also tended to be somewhat higher with blood of low P.C.V., but remained directly related to the plasma viscosity at all P.C.V. levels. When the P.C.V. was below 40% the results obtained at different levels of plasma viscosity with a modified Wintrobe tube of 4·5 mm. internal diameter were much the same as those obtained with the standard tube of 2·5 mm. internal diameter. When the P.C.V. was above that level, however, the larger tube gave results more closely resembling the Westergren readings, though the E.S.R. still tended to fall off at the higher levels of plasma viscosity.

The authors conclude that the discrepancy between the results obtained by the two methods is due to the additive effect on the Wintrobe E.S.R. of a high plasma viscosity and the inadequate bore of the standard Wintrobe tube, the discrepancy being more marked when the P.C.V. is over 40%. *R. F. Jennison*

1251. **The Mechanism of the Fractional Erythrocyte Sedimentation Rate (F.E.S.R.).** (К механизму фракционной реакций оседания эритроцитов (ФРОЭ)) S. M. Gavalov. *Советская Медицина* [*Sovetsk. Med.*] **21**, 62–66, No. 8, Aug., 1957. 2 figs., 10 refs.

In 1926 Epshtein introduced the method of fractional determination of the erythrocyte sedimentation rate (F.S.R.), in which the rate of sedimentation is recorded every 15 minutes over a period of 90 minutes and the results plotted as a curve. The type of curve obtained enables the observer to distinguish five types of E.S.R.: the normal, the areactive, the hyporeactive, the reactive, and the hyperreactive.

The hyperreactive curve, distinguished by rapid sedimentation during the first 30 minutes followed by slowing of the rate, is characteristic of acute infections in a highly reactive subject, for example, in acute rheumatism or pneumonia. The reactive type, in which the most rapid sedimentation occurs in the second or third quarter of the first hour, is found in acute infections in subjects with usually normal reactivity. The hyporeactive curve, in which the highest rate is at the end of the first hour, occurs in convalescent patients or in acute infections in subjects with lowered reactivity. The areactive curve is found in cases of overwhelming infection, or in patients with little or no resistance; in this type the curve is very low and nearly horizontal throughout. In the normal curve, as seen in healthy persons, the rate does not rise above normal levels and successive estimations do not differ by more than 1 to 3 mm. per minute. The author states that it is possible by means of fractional estimation of the E.S.R. to evaluate the stage of the infection and the reactivity of the patient, and the procedure is therefore valuable in prognosis, especially in children.

L. Firman-Edwards

1252. **The Effect of Some Fatty Acids and Phospholipids on Blood Coagulation**

J. R. O'Brien. *British Journal of Experimental Pathology* [*Brit. J. exp. Path.*] **38**, 529–538, Oct., 1957. 1 fig., 21 refs.

This report from the Central Laboratory, Portsmouth and Isle of Wight Area Pathological Service, Portsmouth, describes the results of investigations into the effects of a variety of phospholipids and fatty acids on several blood coagulation systems. The effect of diphosphoinositide, phosphatidyl inositide, phosphatidyl serine, and phosphatidal ethanolamine was similar (in varying degree) to that of platelets on the clotting time, thrombin generation, prothrombin consumption, thromboplastin generation, and the Russell viper venom accelerated clotting time ("stypven" time). Cardiolipin, the acetal of lecithin, and certain free fatty acids reduced the stypven time, but had no effect on the plasma clotting time or on thrombin generation. Other fatty acids reduced both the stypven time and the plasma clotting time. Egg lecithin, sphingosine, and sphingomyelin were found to be inactive. *A. Brown*

1253. **Studies of Hemostatic Mechanisms in Leukemia and Thrombocytopenia**

J. H. Lewis, J. H. Burchenal, R. E. Ellison, J. H. Ferguson, J. H. Palmer, M. L. Murphy, and M. B. Zucker. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **28**, 433–446, Nov., 1957. 8 figs., 15 refs.

In an investigation designed to determine the aetiology of bleeding in leukaemia, carried out at the Sloan-Kettering Institute, New York, and the University of North Carolina, cases of various forms of leukaemia, with and without haemorrhagic manifestations, were studied and the results compared with those in patients with thrombocytopenia resulting from other causes and with those in a small number of patients with thrombocythaemia. A battery of tests of various aspects of the haemostatic mechanism was employed.

Thrombocytopenia was, of course, a frequent finding in leukaemic patients, but this was not well correlated

with clinical evidence of bleeding. Some patients with low platelet counts did not bleed, while others with normal platelet counts did. Estimation of the concentrations of the plasma coagulation components showed that that of Factor V was frequently depressed. In thrombocytopenia from other causes a lowered platelet count was present, but there was no change in the concentration of any of the plasma factors. Comparison of the results of the tourniquet test in leukaemic patients with those in other thrombocytopenic patients with platelet counts in the same range showed that the test gave a normal result in the leukaemic patients, but usually an abnormal one in those with thrombocytopenia; further, the bleeding time was usually prolonged in thrombocytopenia, but in half of the patients with leukaemia it was found to be normal.

The problem was also studied by determination of the thrombin clotting time of plasma and of increased fibrinolysis, and by serotonin assay. [The original should be consulted for the details. Although this investigation failed to produce a complete solution to the problem of bleeding in leukaemia, the paper nevertheless contains much valuable information.] *A. S. Douglas*

1254. **Electron Microscopic Observations on Platelets from Human Blood**

R. V. P. HUTTER. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **28**, 447–460, Nov., 1957. 8 figs., bibliography.

This paper from Yale University describes the appearances under the electron microscope of platelets in heparinized plasma before and after incubation for varying periods at 37° C. on a film of " formvar ".

The various forms of platelet recognized by the author were as follows: " earliest ", dendritic, neuronal, transitional, extended, and " butterfly ". The " earliest " forms were 3 μ in diameter, were smooth-edged, and showed a dense granulomere almost filling the entire platelet, with a narrow hyalomere. With progressive duration of incubation on the film of formvar the platelets spread, this change affecting mainly the hyalomere, so that the ratio of granulomere to hyalomere became reversed. Later, " pseudopodia " of hyaloplasm appeared, to form the dendritic type of platelet. Further centrifugal flow of hyaloplasm resulted in a wider margin of hyalomere with shorter, more blunted projections, representing the neuronal and transitional forms. Finally, as the hyaloplasm flowed further, the extended and " butterfly " forms resulted. Increasing the dosage of heparin appeared to retard the process of spreading of the platelets. The author doubts whether the platelets undergo lysis in contact with thrombin or thromboplastin, or even on coagulation itself. He suggests that the forms previously described as " lysed " are only intact variations of the transitional type of platelet. He considers that platelets may function as an intact entity in the coagulation of blood.

[The paper contains excellent electron micrographs of the appearances of platelets described. The original should be consulted for the details of the techniques employed.] *A. S. Douglas*

MORBID ANATOMY AND CYTOLOGY

1255. **Organisation and Canalisation in Arterial Thrombosis**

J. H. DIBLE. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **75**, 1–7, 1958. 11 figs., 6 refs.

In this paper from the Postgraduate Medical School of London the author states that his purpose is " to put forward evidence that the processes of organisation and canalisation are distinct and independent—in origin, in purpose, in the vascular channels involved, and in effect ".

Microscopical examination of an artery containing a well canalized thrombus in which the vessels have been distended by injection with formalin shows clearly that the canalizing vessels, which lie inside the internal elastic lamina, are longitudinally arranged, whereas the vasa vasorum, which lie external to this lamina, are radially disposed. The author concludes that the internal elastic lamina usually offers an impassable barrier to the ingress of vessels from the vasa vasorum and that canalization of an arterial thrombus takes place without their participation. Examination of a newly formed clot shows that at an early stage the interstices of its spongy structure rapidly become lined with endothelial cells, and circulation of blood through these channels leads to their subsequent development into definitive channels. Reticulin and later collagen fibrils appear around these endothelial spaces. The origin of the endothelial cells is not clear, but the author has found in serial sections that certain endothelium-lined channels in a thrombus are unconnected with the endothelial lining of the vessel, and he suggests that free endothelial cells which have become displaced into the centre of the clot during thrombosis may take part in the formation of these channels by " grafting themselves upon the new fibrin network ".

In certain circumstances the vasa vasorum may erupt through the internal elastic lamina and take part in the revascularization process, but in general it will be found that in such cases the vessel wall is the site of pre-existing disease and the lamina deficient. The more usual situation is that the two systems of vessels, one within and one without the internal elastic lamina, are quite separate, the former serving the purpose of canalization and the latter increasing in size and prominence to supply additional nourishment to the inner part of the arterial wall which is no longer able to supply itself by imbibition. *J. B. Cavanagh*

1256. **Microscopic Properties of Whole Mounts and Sections of Human Bronchial Epithelium of Smokers and Nonsmokers**

SUK CHUL CHANG. *Cancer* [*Cancer (Philad.)*] **10**, 1246–1262, Nov.–Dec., 1957. 11 figs., 27 refs.

In this paper from the National University, Seoul, Korea, and Washington University, St. Louis, Missouri, the author compares and describes the frequency of morphological changes seen post mortem in the bronchial epithelium of 13 male and 21 female non-smokers and of 41 male and 22 female smokers ranging in age from 40 to 86 years; the definition of a smoker was that proposed by Doll and Bradford Hill. Vertical transverse

sections of bronchi were studied and also whole mounts of the bronchial mucosa, these being prepared by an acetic acid maceration method, which is described.

The appearances in whole mucosal mounts are first described [and well illustrated]. In the lungs of the smokers goblet cells were more numerous and a higher proportion of them were distended than in non-smokers, the distension being maximal in heavy smokers' lungs. Study of the whole mounts also revealed the presence of nuclei of ciliated columnar cells and of basal cells. Occasionally the mucosa of heavy smokers showed hyperplasia with no goblet cells but cells with large irregular nuclei which, it is suggested, represents early squamous metaplasia or pre-malignant lesions; no such areas were seen in the non-smokers. A peculiar furrowing was also seen in the mucosa taken from the vicinity of a bronchogenic carcinoma, and the cells showed evidence of nuclear activity. Variations in the appearance of the mucosa of smokers are attributed to different smoking habits or to the use of different brands of tobacco. The author next discusses the appearances in the vertical sections of bronchial epithelium. The trachea and bronchi of the smokers showed pseudostratified ciliated epithelium and the average length of the cilia was shorter than in non-smokers, namely, from 1·4 to 3 μ compared with 3·2 to 4·4 μ. Counts of goblet cells were made on 1,000-μ lengths of epithelium and were found to be significantly higher in smokers; the increased number of these cells is interpreted as a protective mechanism. From a rough quantitative assessment of basal-cell activity based on the number of layers of basal cells it was estimated that 23% of non-smokers as against 43% of smokers and 61% of heavy smokers showed hyperactivity. The average total thickness of epithelium was also significantly higher in smokers.

Epithelial indentations, which were more frequent and larger in smokers' lungs, are described, but no suggestion as to their significance is made; they were not considered to be artefacts. Leucocytic infiltration was equally frequent in both groups. Atypical epithelial cells and squamous and transitional metaplasia were more common in smokers, being found in 37% of the latter. *F. Hillman*

1257. **The Histology of Generalized Pulmonary Emphysema. II. Diffuse Emphysema**
K. H. McLean. *Australasian Annals of Medicine* [*Aust. Ann. Med.*] **6**, 203–217, Aug., 1957. 13 figs., 30 refs.

In a previous paper from the University of Melbourne (*Aust. Ann. Med.*, 1957, **6**, 124; *Abstr. Wld Med.*, 1958, **23**, 238) the author described the histology of the earliest focal lesions of pulmonary emphysema. He now completes his study by dealing with the later or "diffuse" stage. Diffuse emphysema involves dilatation of the air spaces in the whole of the secondary lobule, in contrast to focal emphysema, which affects only the middle portion. In the author's opinion, based on his examination of serial sections of necropsy specimens of 75 lungs, the diffuse form never starts as such, but develops from a previous focal lesion. In most of the cases of preclinical emphysema examined the lesion was essentially focal, but in some lungs evidence of diffuse change was found early in the evolution of the focal lesion in the form of extension of the process of dilatation and destruction of the alveolar walls outwards to the periphery. In other cases diffuse change did not become apparent until the focal lesion was well developed. In most of the cases of clinical emphysema examined, on the other hand, there were extensive diffuse lesions, although focal lesions were still obvious in much of the lung. The basic pathological change is considered to be a non-specific bronchiolitis, and the further evolution of the lesion is discussed at length. An attempt is made to correlate the morbid physiology of pulmonary emphysema with the histological changes, and factors affecting the elasticity of the lung are discussed. Chronic bronchitis is stated to be a frequent, though not a necessary, accompaniment of the condition. In conclusion the various aetiological factors are detailed and the part played by bacteria is discussed. *G. J. Cunningham*

1258. **Vascular Invasion in Bronchogenic Carcinoma**
A. J. Ballantyne, O. T. Clagett, and J. R. McDonald. *Thorax* [*Thorax*] **12**, 294–299, Dec., 1957. 3 figs., 22 refs.

From the Mayo Clinic the authors report the results of a search for evidence of vascular invasion in 59 lungs or pulmonary lobes which had been removed surgically for bronchogenic carcinoma. In each case the vessels were identified at the hilus and systematically opened as far as possible into the tumour. It was often not difficult to find tumour thrombi within the lumen, but when a thrombosed vessel was seen in cross-section it was not always possible to determine with the naked eye whether the thrombus contained tumour tissue. On macroscopical examination alone vessels were considered to be involved by tumour in 28 of the 59 specimens, the intravascular spread being apparently largely towards the hilus. On microscopical examination malignant cells appeared to have a remarkable power of infiltrating through vessel walls, and various degrees of thrombosis within the vessel attended this process, often with invasion of the thrombus by malignant cells. However, the lumen of a vessel evidently does not always provide an ideal site for neoplastic proliferation, the thrombi sometimes appearing to contain necrotic tumour cells.

Of the 59 carcinomata examined, 34 were of the squamous-cell type, and in 27 (80%) of these microscopical evidence of vascular involvement was found. Of the other cases, 10 were of the large-cell and 9 of the small-cell type and 6 were adenocarcinomata; all of these exhibited evidence of vascular involvement. It was thought that arteries had been invaded by the tumour in 10 cases (5 of squamous-cell carcinoma, 2 of adenocarcinoma, and 3 of small-cell carcinoma).

The authors found it impossible to determine whether vascular invasion gave rise to any characteristic symptoms, and there was no apparent relation between the occurrence of invasion and the presence of pulmonary osteoarthropathy or peripheral venous thrombosis. Three of the 59 patients died in the postoperative period,

and necropsy was carried out on 2 of them. In only one case were the regional lymph nodes involved, but in both metastases were found in the brain and adrenal glands, the operation specimen having shown a tumour thrombus in a branch of the pulmonary vein in one case and involvement of a vein 4 mm. in diameter in the other. Of the 56 survivors, 55 were traced, of whom 18 lived for 3 or more years after operation. Of the 7 patients in whom there was no evidence of vascular invasion, 4 survived for 3 or more years; of the remaining 3, one died after an operation for a metastasis in the scapula, one after an operation for astrocytoma, and the third of undetermined causes.

The authors conclude that " the majority of bronchogenic carcinomata have access at some time to the vascular system " and that, whatever the mechanism involved, transport of malignant emboli by the blood accounts for the frequently widespread distribution of metastases in such cases. However, the effect of the dissemination of tumour cells through the blood stream may be nullified either by host resistance or by some inherent inability of the cells to grow in their new environment, and these factors must play a decisive part in determining the course of the disease. Surgical manipulation, as a possible cause of vascular metastasis, should certainly be kept to a minimum and preliminary ligation of veins should be considered as a means of increasing the post-operative survival rate. *R. Wyburn-Mason*

1259. **Changes in the Lung in Uraemia.** (Sulle alterazioni polmonari nell'uremia)
D. Batolo. *Archivio italiano di anatomia e istologia patologica* [*Arch. ital. Anat. Istol. pat.*] **31**, 481–500, 1957. 11 figs., 13 refs.

The author reports, from the University of Messina, a morbid anatomical study of the lungs of 6 patients who died of uraemia (due in 4 cases to subacute or chronic glomerulonephritis, in one to chronic pyelonephritis, and in one to renal arteriolar sclerosis complicated by disease of the prostate) and of 10 rats rendered uraemic by bilateral nephrectomy and killed after periods varying from 24 to 72 hours. In the human cases the lungs were firm and of slightly increased volume, with grey, firm cut surfaces; the oedema was most marked in the hilar regions. Microscopically, most of the alveolar spaces were filled with eosinophilic amorphous material (which reacted strongly with periodic-acid–Schiff and stained blue with azovan), and also with scanty fibrin and a cellular exudate consisting mainly of rather large mononuclear cells. In many cases hyaline membranes lined the alveoli, and in many areas there was histiocytic infiltration of the interalveolar septa. The capillaries and, to a lesser extent, the medium-sized blood vessels showed elongation and tortuosity, swelling of endothelial cells, and hyaline changes in the vessel wall. Essentially similar changes were found in the lungs of the uraemic rats, in which the vessels were also elongated and tortuous, with hyaline changes, frequently showing signs of haemorrhage into the adventitia of both arteries and veins, this probably being due to leakage from the vasa vasorum.

The author discusses the relationship of these changes to the similar pulmonary changes seen in acute rheumatism, interstitial pneumonitis, and chronic congestive cardiac failure. He considers that the changes in capillary permeability are of major significance in the pathogenesis of the uraemic lung. *H. Caplan*

1260. **An Electron Microscope Study of the Glomerulus in Nephrosis, Glomerulonephritis, and Lupus Erythematosus**
M. G. Farquhar, R. L. Vernier, and R. A. Good. *Journal of Experimental Medicine* [*J. exp. Med.*] **106**, 649–660, Nov. 1, 1957. 11 figs., 34 refs.

The structure of the renal glomeruli was examined by the light and electron microscopes in biopsy material from 76 children suffering from nephrosis, glomerulonephritis, and lupus erythematosus. It is pointed out that the normal glomerulus has three components—the endothelium, basement membrane, and epithelium. In the patients with nephrosis there was a loss of the characteristic organization of the epithelial cytoplasm into foot processes. (This was especially marked, and appeared to be the only change, in cases of " pure " nephrosis.) The capillary loop surfaces were covered by broad masses of epithelial cytoplasm. There was also an increase in the number of vacuoles. Swollen endothelium with numerous intracytoplasmic vesicles and some changes in the basement membrane were observed. The glomeruli in glomerulonephritis showed mainly proliferative changes of the endothelium and basement membrane. In the acute stage of the disease the number of endothelial cells was increased; in addition cytoplasmic swelling of both endothelium and epithelium and thickening of the basement membrane with accumulations of " basement-membrane like " material were seen. In the subacute and chronic stages the glomeruli consisted of tangled masses of cells with few open blood channels. The most characteristic finding in lupus erythematosus was a thickening of the basement membrane with some endothelial proliferation. This could be seen before any sign of the " wire-loop " by light microscopy; similarly the changes in nephrosis were seen by the electron microscope before they were detected by the conventional microscope.

In the later stages of these three disease conditions no distinction between them was possible by the electron microscope, the appearances in all three being very similar. As expected, there was a considerable overlap in the appearances in many of the cases. *G. Loewi*

1261. **The Pathology of Armanni–Ebstein Diabetic Nephropathy**
S. Ritchie and D. Waugh. *American Journal of Pathology* [*Amer. J. Path.*] **33**, 1035–1057, Nov.–Dec., 1957. 11 figs., 21 refs.

Armanni–Ebstein nephropathy is a complication of diabetes mellitus in which localized accumulations of glycogen are found in certain areas of the kidney tubular system. The investigation described in this paper from McGill University, Montreal, was directed primarily towards determining the location of the change in the

renal tubules by micro-dissection of individual nephrons in kidneys obtained at necropsy from 5 cases of Armanni–Ebstein diabetic nephropathy. In each case routine sections showed that abundant glycogen was present in tubules situated on either side of the cortico-medullary junction, and that transition from normal to diseased cells along the tubule might be abrupt. Micro-dissection of the nephrons revealed that the proximal convoluted tubule was the invariable site of the glycogen deposition, usually the terminal straight portion just above its continuation into Henle's loop. The change might be focal or continuous along this region. A notable finding was the absence of involvement of those nephrons which did not penetrate the cortico-medullary region; possible reasons for this and also for the metabolic derangement are briefly discussed. *J. B. Cavanagh*

1262. **The Nature of Diabetic (Kimmelstiel–Wilson) Glomerulosclerosis**
M. J. G. Lynch and S. S. Raphael. *Diabetes* [*Diabetes*] 6, 488–497, Nov.–Dec., 1957. 14 figs., bibliography.

At the General Hospital, Sudbury, Ontario, the authors studied the glomerular lesions in 7 cases of diabetic nephropathy, various staining techniques being applied to sections of kidney tissue. The presence of free and diffuse haemoglobin in all types of glomerular lesion in formalin-fixed material was deduced from the positive staining reaction obtained by the benzidene–nitroprusside, "nadi", dithizone (diphenylthiocarbazone), and Fischler staining methods. Many of the lesions appeared to be micro-aneurysmal in character and commonly contained intact or fragmented erythrocytes.
A. Wynn Williams

1263. **Characteristics of Leukocytes in the Urine Sediment in Pyelonephritis. Correlation with Renal Biopsies**
K. P. Poirier and G. G. Jackson. *American Journal of Medicine* [*Amer. J. Med.*] **23**, 579–586, Oct., 1957. 5 figs., 10 refs.

When a urinary sediment is treated with a supravital stain dead leucocytes are stained dark, whereas relatively healthy cells are stained a pale colour or not at all and may show Brownian movement of the cytoplasmic granules. The authors have used this method in the examination of urine from a series of patients under investigation for pyuria, the stain employed being a mixture of safranin and gentian violet.

Of 21 cases of pyelonephritis proven by biopsy, pale-staining cells were found in the urine in 18. In the other 3 only a single specimen of urine had been examined. Of 11 cases in which the kidneys were normal on biopsy, only in 4 were pale-staining cells found in the deposit, and in these there was clinical or radiological evidence of pyelonephritis. Of a further 7 patients, apparently not included in the above series, who had histological evidence of pyelonephritis but whose urine contained no pale-staining cells, 2 had chronic healed pyelonephritis, 4 had recently received antibiotics, and one had a mild form of the disease.

The authors point out that the finding of pale-staining cells in urine appears to be of diagnostic importance, suggesting that the pyuria is due to pyelonephritis rather than to disease of the lower urinary tract. Examination of the urinary sediment for such cells would be particularly useful in detecting early or subacute pyelonephritis, when pyuria may not be marked. *M. C. Berenbaum*

1264. **Further Studies on the Lymphatic Vessels at the Hilus of the Liver of Man: Their Relation to Ascites**
A. H. Baggenstoss and J. C. Cain. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **32**, 615–627, Oct. 30, 1957. 4 figs., 15 refs.

In continuation of their studies on the number of lymphatic vessels in the hilum of the liver as seen post mortem in relation to the presence or absence of ascites and hepatic cirrhosis (*New Engl. J. Med.*, 1957, **256**, 531; *Abstr. Wld Med.*, 1957, **22**, 250) the authors, working at the Mayo Clinic, have examined a further series of cases, using the same methods as before.

Analysis of the results obtained in 41 additional cases of ascites without cirrhosis together with those previously reported (bringing the total to 69) shows that there was a significant increase in the mean number and size of the lymphatic vessels in the hepatoduodenal ligament when the ascites was associated with congestive heart failure (34 cases), lupus erythematosus (3 cases), viral hepatitis (2 cases), or massive neoplastic invasion of the liver (2 cases) as compared with the findings in 100 consecutive necropsies on subjects without ascites or cirrhosis. In contrast, no such increase was found in ascites due to renal disease (7 cases) or neoplastic involvement of the peritoneum (9 cases). (The remaining 12 cases formed a miscellaneous group in which no single factor could account for the ascites.) The findings in 19 additional cases of cirrhosis, with or without ascites, confirmed those in the 40 previous cases, the mean number of lymphatic vessels in the hepatoduodenal ligament being increased regardless of the cause of the cirrhosis.

No relationship was found between the number and size of the lymph nodes in the hepatoduodenal ligament and the number of lymphatic vessels, the number of nodes being approximately the same in all the above categories and there being no increase in the number of vessels in cases of leukaemia and lymphoma with involvement of the hilar nodes. Microscopical examination of the lymph nodes revealed an excess of intra- and extracellular lipid in many cases, especially those of alcoholic cirrhosis. The authors suggest that the lymphatic vessels may be an important path of mobilization of fat from its stores in the liver, the high incidence of lipid deposits in the nodes in cases of alcoholic cirrhosis being related to the fatty change in the liver frequently associated with this condition. A pilot study of 10 cases showed that lymph nodes from the porta hepatis contained more lipid than lymph nodes from other parts of the body.
I. Berkinshaw-Smith

1265. **The Neuropathology of Hereditary Optic Atrophy (Leber's Disease); the First Complete Anatomic Study**
J. Kwittken and H. D. Barest. *American Journal of Pathology* [*Amer. J. Path.*] **34**, 185–207, Jan.–Feb., 1958. 19 figs., 20 refs.

Microbiology and Parasitology

1266. **Penicillinase Production by *Staphylococcus aureus* Strains from Outbreaks of Food Poisoning**
M. T. PARKER and S. P. LAPAGE. *Journal of Clinical Pathology* [*J. clin. Path.*] **10**, 313–317, Nov., 1957. 23 refs.

The incidence of penicillin-resistant strains of *Staphylococcus aureus* in cultures from cases of food poisoning was investigated at the Public Health Laboratory, Manchester. It was found that 21 out of 24 strains of *Staph. aureus* cultured in recent outbreaks of food poisoning and 8 out of 13 cultured in outbreaks before 1941 were penicillin-resistant and produced penicillinase. All 37 strains were found to be of Phage Group III.

An analysis of the findings in a separate investigation of 1,494 strains of *Staph. aureus* isolated from a variety of human lesions and from nose swabs between September, 1953, and July, 1956, showed that only 45% of all the Group-III strains from sources other than hospitals were penicillin-resistant, whereas the comparable incidence in hospital patients was 86%. There was no significant difference between the proportion found to be resistant in the various types of lesion and in the nasal swabs. *E. G. Rees*

1267. **The Incidence of Pathogenic *Escherichia coli* in Routine Faecal Specimens**
D. R. GAMBLE and K. E. K. ROWSON. *Lancet* [*Lancet*] **2**, 619–621, Sept. 28, 1957. 10 refs.

It is pointed out that little information is available concerning the over-all incidence of *Escherichia coli* in faecal specimens examined at any given laboratory, since it has hitherto been the practice to look for this organism only in specimens from patients under the age of 2 years. Over a period of one year all faecal specimens sent to the Central Public Health Laboratory, Colindale, London, were examined for the presence of *E. coli* of the types usually associated with gastro-enteritis in children. It was found that 13 (5%) out of 243 hospital patients, 18 (2%) out of 943 patients at home, and 67 (25%) out of 273 children in nurseries were excreting one or other of these types. Only 2 of the 13 patients in hospital and 5 of the 18 at home were free from gastro-intestinal symptoms. The authors consider that between 1% and 2% of the adult population are excreting these types of *E. coli*. *R. Hare*

1268. **The Sensitizing Power of Diphtheria Prophylactics in Relation to Poliomyelitis**
S. BEN-EFRAIM and D. A. LONG. *Lancet* [*Lancet*] **2**, 1033–1035, Nov. 23, 1957. 2 figs., 10 refs.

A report by a committee of the Medical Research Council (*Lancet*, 1956, **2**, 1223; *Abstr. Wld Med.*, 1957, **21**, 291) showed that recently preceding diphtheria immunization not only determines the site of possible future paralysis due to poliomyelitis, but predisposes the recipient to it, the risk being greatest with alum-precipitated (A.P.) diphtheria–pertussis vaccine. In their studies at the National Institute for Medical Research, Mill Hill, London, the authors have noted the apparent correlation between the sensitizing power of various diphtheria prophylactics and their ability to predispose to paralytic poliomyelitis, those with a low sensitizing power in guinea-pigs being associated with a low incidence of paralysis in man.

In this paper they describe a method of assaying hypersensitivity to diphtheria toxoid. Groups each of 15 guinea-pigs were sensitized by a single injection of international standard and laboratory standard formol toxoid (F.T.) and A.P. toxoid (A.P.T.)—preparations of diphtheria prophylactics in current clinical use—and of pertussis vaccine, alone or in various combinations, each in appropriate doses. After 28 days the sensitivity of these guinea-pigs to an injection of F.T. was measured by a skin test (the basis of which is briefly outlined), the resulting reaction being a measure of the immediate (Arthus type), delayed (tuberculin type), and total allergic damage. The results were assessed by the method of standard regression analysis and are presented graphically. Soluble antigens were shown to produce a very low degree of sensitization unless pertussis vaccine had been added, whereas the adsorbed antigens produced a high degree of sensitivity.

In order to determine whether antigens that sensitized well also caused more damage when injected into a fully sensitized animal, a second series of guinea-pigs were sensitized with A.P.T. and challenged 28 days later with an injection of F.T. alone or with 1,000 million or 250 million *Haemophilus pertussis* organisms. F.T. and toxoid antitoxin floccules (T.A.F.) caused little sensitivity to toxoid, but aluminium phosphate precipitated diphtheria toxoid (P.T.A.P.) produced maximum sensitivity, about six times greater than with A.P.T. It was also shown that the addition of pertussis vaccine to A.P.T. or to F.T. (which by itself sensitized only a little) resulted in maximal sensitivity to the challenging dose of toxoid.

Finally the authors refer briefly to the special power of pertussis vaccine to render mice susceptible to the action of histamine, to total body irradiation, and to bacterial infection. Pertussis vaccine alone produced a maximal response in sensitized and non-sensitized guinea-pigs in this series. The analogy between the sensitizing power of diphtheria prophylactics in guinea-pigs and their reported paralysis-inducing power in cases of poliomyelitis is therefore clear. *F. Hillman*

1269. **A Heat Labile Haemosensitin from *Mycobacterium tuberculosis* (var. *Rumanis*).** [In English]
S. V. BOYDEN, E. SORKIN, and H. C. ENGBAEK. *Acta pathologica et microbiologica Scandinavica* (*Acta path. microbiol. scand.*) **42**, 153–163, 1958. 22 refs.

Pharmacology and Therapeutics

1270. Effect of Histamine on Gastric Peptic Secretion in Man

E. FRIEDMAN, I. POLINER, and H. M. SPIRO. *New England Journal of Medicine* [*New Engl. J. Med.*] **257**, 901–906, Nov. 7, 1957. 14 refs.

The effect of histamine on gastric pepsin secretion in healthy subjects was studied at Yale University School of Medicine, New Haven, Connecticut, and for this purpose a constant flow of gastric secretion was evoked by subcutaneous injection of 0 5 or 1 mg. of histamine base at 30-minute intervals. Samples of gastric juice were collected every 15 minutes and the *p*H and pepsin concentration determined.

Pepsin output was stimulated in most of the subjects by administration of histamine over a period of at least 2½ hours, the response being proportionately greater in those with low or normal basal secretory activity than in those with hypersecretion. In a few patients a marked increase in the volume of gastric juice produced a fall in pepsin concentration, but the total pepsin output still rose. In the authors' view the findings indicate that pepsinogen does not "accumulate in the intercellular channels of the stomach to be washed out passively". The measurement of total pepsin output is thus more important than the measurement of the pepsin concentration, since the latter may decrease when there is marked outpouring of acid from the parietal cells.

G. B. West

1271. Action of Nicotine on the Heart

J. H. BURN and M. J. RAND. *British Medical Journal* [*Brit. med. J.*] **1**, 137–139, Jan. 18, 1958. 2 figs., 9 refs.

In experimental work in the Department of Pharmacology, University of Oxford, on the action of nicotine on the heart, isolated rabbit auricles were suspended in a bath containing McEwen's solution aerated with oxygen and carbon dioxide at 30° C. When nicotine was added to the bath in the presence of atropine it caused an increase in the amplitude and rate of beating of the auricles. There seemed to be two possible explanations for this: (1) the nicotine stimulated ganglionic tissue in the auricles, the post-ganglionic fibres of which were adrenergic; or (2) nicotine stimulated chromaffin tissue in the auricle, releasing adrenaline and noradrenaline. Earlier work by Kottegoda had shown that hexamethonium bromide blocked the stimulant action of nicotine on the auricles, and this suggested that the action was on ganglionic tissue. In experiments described in the present paper the adrenaline and noradrenaline content of the auricles was reduced by pretreating the animals with reserpine (1·5 mg. per kg. body weight by intraperitoneal injection followed 24 hours later by 5 mg. per kg. intravenously). The auricles from these reserpine-treated animals did not beat so fast as the auricles from untreated animals, but the amplitude of the beat was greater. Nicotine did not increase the rate and amplitude of the beat in auricles from reserpine-treated animals as it did in untreated controls. These results indicate that nicotine stimulates isolated rabbit auricles by releasing adrenaline and noradrenaline, but the mechanism of the release is obscure. The effect of smoking on the heart is discussed. *P. A. Nasmyth*

1272. Study of a Long-acting Quinidine Preparation: Experience in Normal Subjects and in Patients with Myocardial Abnormality

S. BELLET, D. FINKELSTEIN, and H. GILMORE. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 750–758, Nov., 1957. 4 figs., 11 refs.

Quinidine has proved valuable in the treatment and prevention of cardiac arrhythmia of various types, but has the disadvantage that its concentration in the plasma falls rapidly, so that frequent dosage is required. The authors have therefore investigated the action of quinidine gluconate in experiments carried out at Philadelphia General Hospital and the Graduate Hospital of the University of Pennsylvania on 10 healthy subjects. The dose of this long-acting preparation of quinidine used was 1 g. (0·62 g. of the alkaloid). Serial estimations showed an average peak plasma concentration of the drug of 4·34 mg. per litre in an average time of 4·8 hours, this level being maintained for the next 4 to 5 hours; at the end of 12 and 24 hours the plasma levels had fallen to 2·39 and 1·07 mg. per litre respectively. When two doses, each of 1 g., were given at a 10-hour interval in a 24-hour period the average peak level 4 hours after the initial dose was 3·81 mg. per litre, with a somewhat higher level after the second dose, followed by a more gradual fall to levels of 2·66 and 1·24 mg. per litre at 24 and 36 hours respectively after the initial dose. In 5 patients with congestive cardiac failure the drug appeared to produce higher and more sustained plasma levels. The authors have now used this preparation in the treatment of 30 patients with cardiac arrhythmias, including extrasystoles and atrial tachycardia, flutter, and fibrillation, with results similar to those obtained with quinidine sulphate, but with fewer episodes of ectopic rhythm. *I. Ansell*

1273. Clinical Experience with G-23350 (Sintrom)

R. JOHNSON and Y. CHARTIER. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **77**, 756–761, Oct. 15, 1957. 5 figs., 3 refs.

The efficacy of "sintrom" (nicoumalone), a new oral anticoagulant resembling dicoumarol and ethyl biscoumacetate, was studied at the Notre-Dame Hospital, Montreal, in 50 patients (31 males and 19 females) suffering from a variety of conditions including myocardial infarction, ischaemia, rheumatic heart disease, and thrombophlebitis. Prothrombin time was determined

by a one-stage method at the bedside, and the result, obtained in seconds, was expressed as a percentage, the therapeutic level aimed at being 20 to 40% (at least 2½ times the normal clotting time). Sintrom was given in an initial dosage of 20 to 28 mg. and a daily maintenance dosage of 2 to 12 mg., the duration of treatment being 10 to 40 days. A stable prothrombin level of 20 to 40% was achieved in 35 of the patients within 48 hours of the start of treatment, and in 24 out of 25 patients tested the prothrombin level returned to normal within 72 hours of withdrawal of the drug. To attain the therapeutic level a higher dosage was required in 7 cases and a lower dosage in 6. Haemorrhagic incidents associated with low prothrombin levels occurred in 3 cases, one of which was fatal. Concurrent administration of chlorpromazine, salicylates, and broad-spectrum antibiotics appeared to enhance the action of sintrom. No case of gastro-intestinal intolerance was seen.

The authors conclude that sintrom has a predictable action, has no cumulative or toxic effects, is easy to administer, and is superior in action to ethyl biscoumacetate. *Gerald Sandler*

1274. **Parenteral Iron Therapy. With Special Reference to a New Preparation for Intramuscular Injection**
P. R. McCURDY, C. E. RATH, and G. E. MEERKREBS. *New England Journal of Medicine* [*New Engl. J. Med.*] **257**, 1147–1153, Dec. 12, 1957. 11 refs.

At the District of Columbia General Hospital (Georgetown University School of Medicine), Washington, D.C., the iron–dextran complex " imferon " was administered to 60 patients suffering from iron-deficiency anaemia. Treatment was begun with small doses, and after administration of 500 mg. of elemental iron the reticulocyte count and the haematocrit were re-determined. If an initial response was noted the total dose was given to in-patients in a rapid course—one or two injections daily—and to out-patients over a longer period—one injection weekly. The total dose was calculated from the formula

$$\frac{(H_n - H_p)}{4} \times 250 + 750 = D_t$$

where H_n and H_p are the normal and the patient's haematocrit values respectively and D_t the total dose in mg. of elemental iron.

The results of treatment in uncomplicated cases were uniformly good. When a good response was not obtained a complicating disease was usually found or the anaemia proved to be due to a cause other than iron deficiency. The only frequent untoward reactions were pain at the injection site and, in 5 cases, discoloration of the skin. The results were similar to those obtained with iron preparations given orally. The iron–dextran complex is recommended for parenteral iron treatment in: (1) patients who are intolerant of oral iron therapy; (2) patients with chronic bleeding lesions in whom there is a need to create iron stores; and (3) patients with the sprue syndrome or those who have undergone gastrectomy and cannot absorb iron adequately by mouth.
Bernard Isaacs

1275. **Absorption Studies on Radioactive Iron–Dextran in Pregnancy**
L. A. J. EVANS and N. W. RAMSEY. *Lancet* [*Lancet*] **2**, 1192–1196, Dec. 14, 1957. 10 figs., 8 refs.

In this study of the absorption of iron–dextran in pregnancy, reported from Charing Cross Hospital, London, the authors used an iron–dextran preparation similar to the commercial product " imferon " labelled with radioactive iron (^{59}Fe), the rate of absorption from the site of injection in the gluteal muscle being studied over long periods in 8 pregnant women, who received doses of 4 to 8 μc. of ^{59}Fe. Surface counting over the injection site, regional lymph nodes, liver, and spleen was carried out (possible fallacies being discussed) and blood and plasma radioactivity estimated.

It was found that 50 to 60% of the " injected activity " left the injection site within 3 days. The plasma radioactivity was at its maximum after 30 hours and the activity in the erythrocytes steadily increased. About 80% of the dose of the iron–dextran complex was absorbed within 3 weeks of injection, but continuing slow absorption proceeded for as long as 6 months. Appreciable radioactivity was detected in the regional lymph nodes. The authors describe one case, in a patient with polyarthritis, in which, they suggest, poor absorption was due to immobilization and restricted lymph flow. Activity over the liver and spleen was at a maximum between 10 and 20 days. *I. McLean Baird*

1276. **Experience with the Anticoagulant Marcumar**
R. E. ENSOR and H. R. PETERS. *Annals of Internal Medicine* [*Ann. intern. Med.*] **47**, 731–743, Oct., 1957. 5 refs.

In this report from the University of Maryland School of Medicine, Baltimore, the authors present an evaluation of the efficacy of the long-acting anticoagulant " marcoumar " (3-(1-phenylpropyl)-4-hydroxycoumarin) as observed in the treatment of 56 cases of myocardial infarction and 24 of acute phlebitis, and when administered prophylactically in 395 postoperative cases, including 91 patients subjected to operations on the bowel, stomach, or gall-bladder, as well as 716 puerperal cases. In cases of coronary occlusion and acute phlebitis an initial loading dose of 30 mg. on the first day was followed on the third day by the maintenance dose, which ranged from 3 mg. (in cases showing a satisfactory lowering of blood prothrombin level) to 12 mg. daily in resistant cases. In the postoperative and puerperal cases the initial dose was 24 mg., but this was reduced to 21 mg. during very hot weather following the observation that in such conditions some patients show greater sensitivity to the drug.

With this regimen satisfactory reduction in prothrombin concentration was produced in the majority of cases; the highest percentage of unsatisfactory results occurred in patients with myocardial infarction. Among the postoperative patients, one developed melaena and haematemesis following a partial gastrectomy; the bleeding was arrested after the transfusion of one pint (473 ml.) of blood and the injection of 25 mg. of vitamin K_1 intravenously, anticoagulant therapy being stopped,

but the patient died 10 days later of pulmonary embolism. Of the remaining postoperative cases, bleeding occurred in 4, but was never severe enough to require blood transfusion, the intravenous administration of vitamin K_1 (in 2 cases) being sufficient to arrest the haemorrhage.

In a comparative study of the results of the long-term out-patient treatment of survivors of coronary occlusion the authors also found marcoumar superior to other anticoagulants. They state that the advantages of this drug, namely, its prolonged duration of action and the more stable and satisfactory type of prothrombin curve obtained with it, far outweigh its initial delay in action. However, they stress that heparin should be used rather than the short-acting anticoagulants when a quick response is required, even in cases of coronary occlusion of some days' standing. *H. F. Reichenfeld*

1277. **Intramuscular Administration of the Anticoagulant Warfarin (Coumadin) Sodium**

S. SHAPIRO and F. E. CIFERRI. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **165**, 1377–1380, Nov. 16, 1957. 4 figs., 13 refs.

Warfarin (" coumadin ") is stated by the authors to be the first synthetic anticoagulant which can be given intravenously, intramuscularly, and rectally as well as orally. In this study, reported from New York University College of Medicine, 35 adult patients suffering from various thrombo-embolic conditions or myocardial infarction were given a single intramuscular injection of 75 mg. of warfarin in distilled water. A therapeutic range of hypoprothrombinaemia was reached in 24 hours after the injection and lasted as long as 5 days in some cases. The drug can be mixed with heparin, which may be needed to give an immediate anticoagulant effect, though it was not used in this series. *G. S. Crockett*

1278. **Clinical Observations on Use of Warfarin (Coumadin) Sodium, a New Anticoagulant**

R. E. FREMONT and B. JAGENDORF. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **165**, 1381–1388, Nov. 16, 1957. 7 figs., 17 refs.

At Brooklyn Veterans Administration Hospital, New York, 85 male patients, whose ages ranged from 32 to 80 and the majority of whom were suffering from acute myocardial infarction, were treated with warfarin by mouth. This synthetic anticoagulant is highly soluble in water and is chemically related to dicoumarol; its prothrombin-reducing effect can be counteracted by the administration of phytonadione (vitamin K_1). The usual initial dose was 50 mg., with a subsequent daily maintenance dose of 5 to 15 mg. according to the blood prothrombin level. The drug appears to exert a smooth anticoagulant effect, and when given by mouth the therapeutic hypoprothrombinaemic range is reached in 36 to 48 hours.

The authors consider this drug to be the most useful anticoagulant at present available because of its predictable and consistent effects, which, they suggest, may be related to its solubility in water. An excessive depression of prothrombin production was encountered in only 3 cases. *G. S. Crockett*

1279. **Clinical and Laboratory Observations on Chlorothiazide (Diuril). An Orally Effective Nonmercurial Diuretic Agent**

R. V. FORD, J. H. MOYER, and C. L. SPURR. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 582–596, Oct., 1957. 12 figs., 6 refs.

A study of the action in human beings and laboratory animals of the new diuretic chlorothiazide (" diuril ") is reported from the Veterans Administration Hospital and Baylor University College of Medicine, Houston, Texas. Intravenous administration of the drug to 34 dogs resulted in a water diuresis, a large output of sodium and chloride in about equal quantities, and a smaller increase in potassium and bicarbonate excretion; the output of ammonia fell, and the *p*H of the urine rose. There was no increase in the glomerular filtration rate, the drug acting, therefore, on the tubules.

Similar changes were observed when the drug was given by mouth to 10 patients who had had congestive cardiac failure and were free from oedema. The effect was maximal between the second and fourth hours and persisted for about 12 hours. The effective dose was 1 to 2 g., no enhancement being observed with higher doses. The authors state that there was no evidence of toxicity with a dose of 4 g. Oral administration resulted in a greater loss of electrolytes and fluid than did intravenous administration of the same dose of the drug. In studies on single patients it was noted that 2 or 4 fractional doses during the day were more effective than a single large dose, and that a diuresis could be maintained by giving 1 to 2 g. each day, indicating that no renal tolerance developed. No toxic effects occurred in 20 patients with congestive heart failure given chlorothiazide in a daily dose of 0·25 to 2 g. for 3 months. Metabolic acidosis did not develop, nor was there gross depletion of potassium.

By means of dose–response curves the potency of chlorothiazide was compared with that of mercurial preparations given parenterally and by mouth; chlorothiazide was found to be twice as potent as acetazolamide (" diamox ").

[This is a valuable study, and appears to confirm the claim that chlorothiazide has definite advantages over mercurial diuretics and carbonic anhydrase inhibitors.] *T. B. Begg*

1280. **The Effect of Morphine Sulfate upon the Renal Excretion of Water and Solute in Man**

S. PAPPER, L. SAXON, M. B. BURG, H. W. SEIFER, and J. D. ROSENBAUM. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **50**, 692–704, Nov., 1957. 3 figs., 28 refs.

The effect of morphine on urine flow, glomerular filtration rate, and solute excretion in 16 healthy subjects was studied at the Boston University School of Medicine. A water load was established on 22 occasions in these 16 subjects by administration of 20 ml. of tap water per kg. body weight, this load being maintained by giving water after each voiding of urine to bring the body weight up to that obtaining after the initial loading. The subjects remained recumbent except when voiding urine, which

was usually collected at intervals of up to 30 minutes. After two periods of "maximal diuresis" morphine sulphate was administered subcutaneously in a dosage of 7·5 to 30 mg. or intravenously in a dosage of 5 to 10 mg. Venous blood was obtained at the height of the diuresis and after the experiment. The blood and urinary concentrations of sodium, potassium, chloride, and creatinine were estimated and total osmolarity was determined by freezing-point measurement. Inulin and PAH clearances were estimated in 2 subjects. The equations given by Smith (*Fed. Proc.*, 1952, **11**, 701) were used to calculate osmolar and free water clearances.

In 17 experiments morphine caused a fall in the flow or urine of more than 2 ml. a minute, which was not accompanied by a rise in the osmolarity of the urine. There was a decrease in the endogenous creatinine clearance and in the rate of total solute excretion. In 7 experiments a late fall in the flow of urine associated with a rise in osmolarity was noted. The decrease in diuresis could be attributed to a decrease in the glomerular filtration rate and the rate of solute excretion.

It is concluded that in healthy subjects therapeutic doses of morphine cause a decrease in the rate of water diuresis without evident release of antidiuretic hormone.

Norval Taylor

1281. **The Effect of Dihydrocodeine upon Respiration and Circulation in Man**

J. E. ECKENHOFF, M. HELRICH, and W. D. ROLPH. *Anesthesiology* [*Anesthesiology*] **18**, 891–896, 5 refs.

The effect of dihydrocodeine upon the respiration and circulation of healthy subjects was studied at the University of Pennsylvania School of Medicine, Philadelphia.

In doses of 50 to 75 mg. injected intramuscularly the drug produced a slight depression of respiratory rate and minute volume, and a tendency to hypotension which became pronounced to the point of fainting in 3 cases when the subject was tilted 50 to 60 degrees in the head-up position.

W. Stanley Sykes

1282. **Effects of Bemegride on Barbiturate Overdosage in Humans**

S. GERSHON and F. H. SHAW. *British Medical Journal* [*Brit. med. J.*] **2**, 1509–1514, Dec. 28, 1957. 2 figs., 26 refs.

In this paper from the Department of Pharmacology, University of Melbourne, an investigation is reported of the effects of bemegride by mouth on barbiturate overdosage. A number of psychiatric patients were given increasing doses of a barbiturate, with bemegride added in the proportion of 10 to 25% of the total dosage given. Pentobarbitone sodium was given to 13 patients and phenobarbitone sodium to 37, the doses being initially 100 mg. of pentobarbitone and 250 mg. of phenobarbitone increasing by 25% every 3 days; the highest doses given (2 cases) were 2,333 mg. of pentobarbitone and 2,666 mg. of phenobarbitone. Amiphenazole, which was tried in some cases, appeared to have little effect. It was found that the addition of bemegride delayed the onset of sleep but that with the larger doses of the barbiturate sleep lasted longer. Bemegride was a more effective antidote against phenobarbitone than against pentobarbitone. It did not give rise to convulsions even in large doses, but in the authors' view it should not be given to epileptics. After the larger doses of barbiturate there were signs of overdosage for one or more days following ingestion, although these signs were minimal on the first day of treatment.

V. J. Woolley

1283. **Modification of Barbiturate Sleep Treatment by the Use of Bemegride**

E. M. TRAUTNER, T. W. MURRAY, and C. H. NOACK. *British Medical Journal* [*Brit. med. J.*] **2**, 1514–1518, Dec. 28, 1957. 15 refs.

The effect on the depth and duration of narcosis of the addition of bemegride to barbiturates was studied in 12 healthy volunteers and 13 patients at Sunbury Mental Hospital, Victoria, Australia. The first group received 65 to 520 mg. of a barbiturate with added bemegride in the proportion of 12 to 23% of the total dosage. Tests were carried out with various barbiturates combined with other analeptics, but the latter drugs were inferior to bemegride. To the second group, all schizophrenic patients, phenobarbitone, pentobarbitone, and amylobarbitone were given with 12% of bemegride. The results obtained with amylobarbitone, which are tabulated, closely resembled those obtained with phenobarbitone and pentobarbitone. [The authors give details only of the response to amylobarbitone; for the results with the two other barbiturates see Abstract 1282.] Up to a dosage of 750 mg. with 12% of bemegride the effect of the barbiturate was not modified. In a dosage of 1 to 1·5 g., also with 12% of bemegride, the duration and depth of sleep were reduced, but there was no hangover or drowsiness; doses of 1·5 to 3 g. had much less effect. Sedation persisted for 1 to 3 days, and no undesirable after-effects were noted.

V. J. Woolley

1284. **Analgesic Effectiveness of Orally Administered Ethoheptazine in Man**

R. C. BATEMAN, M. GOLBEY, A. J. GROSSMAN, and P. LEIFER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **234**, 413–419, Oct., 1957. 5 refs.

A trial of a new synthetic compound, ethoheptazine, an analogue of meperidine, was carried out at the Metropolitan Hospital (New York Medical College), New York, on patients who required analgesics for a variety of surgical and medical conditions. First a group of 107 ambulatory patients were given 50 mg. of ethoheptazine 4 times a day for periods ranging from one day to 10 weeks, half of them being treated for at least 2 weeks. Analgesia was considered satisfactory in 73%; mild side-effects occurred in only 4 cases. Next a series of 140 hospital patients were given either 50 or 100 mg. of ethoheptazine orally either 4 times a day or every 4 hours, or as necessary, the duration of therapy ranging from 1 to 285 days; 49% were treated for one week or less. The dose of 50 mg. was found to be inadequate, but 100 mg. gave satisfactory analgesia in 62% of trials. Side-effects were again noted in only 4 cases.

Ethoheptazine was also tried in the management of post-partum pain. In response to a dose of 100 mg.

given every 4 hours analgesia was considered satisfactory in 82% of 83 cases. Finally a combination of 50 mg. of ethoheptazine and 300 mg. of aspirin was tested in ambulatory patients suffering from pain due to musculoskeletal conditions, and double this dosage in women post partum. In the former group the results were identical with those observed with ethoheptazine alone; for post-partum pain, however, the combination gave results which were superior to those of ethoheptazine alone. *Mark Swerdlow*

1285. **The Bronchomotor Effects of Certain Intravenous Barbiturates on Vagal Stimulation in Dogs**
M. L. BERNSTINE, E. BERKER, and M. CULLEN. *Anesthesiology* [*Anesthesiology*] **18**, 866–870, Nov.–Dec., 1957. 1 fig., 5 refs.

Reports in the literature on the bronchomotor effects of the ultra-short-acting barbiturates, measured on isolated muscle strips, in guinea-pigs, and in cats, are conflicting. The authors have therefore carried out further investigations at the Albert Einstein Medical Center, Philadelphia, with thiopentone and hexobarbitone ("evipan"), using dogs under intravenous chloralose anaesthesia. The vagus nerve was exposed and cut in the neck, and the minimum electrical stimulation that would elicit bronchiolar constriction, as recorded by the Karzett–Rössler method, was determined. A dose of one or other barbiturate, varying from 5 to 55 mg. per kg. body weight, was then given and the measurement repeated. Blood pressure was recorded simultaneously from a cannula in the carotid artery.

Both drugs caused a reduction in carotid arterial pressure, and both were shown to be capable of blocking the bronchoconstriction (and bradycardia) elicited by vagal stimulation. However, the latter effect was observed in only half of the dogs, irrespective of the dose of barbiturate given. It is suggested that the bronchomotor effects of these drugs in man are probably similarly variable between individuals. *W. Stanley Sykes*

1286. **Neuromuscular Effects of Ether, Cyclopropane, Chloroform and Fluothane**
D. C. WATLAND, J. P. LONG, C. B. PITTINGER, and S. C. CULLEN. *Anesthesiology* [*Anesthesiology*] **18**, 883–890, Nov.–Dec., 1957. 5 figs., 11 refs.

In its peripheral neuromuscular blocking effect ether acts synergistically with curare, but the fact that small repeated doses of neostigmine will reverse the blocking activity of the latter while accentuating that of the former indicates that the two drugs differ in their mode of action. At the State University of Iowa College of Medicine, Iowa City, the authors have investigated the peripheral neuromuscular activity and the effect on the action of curare of a number of anaesthetic agents in addition to ether.

Anaesthesia with ether reduced the size of the contractions produced in the gastrocnemius muscle of the rabbit by single-shock and tetanic stimulation of the sciatic nerve, the response diminishing progressively as the depth of anaesthesia increased. Curare given during anaesthesia produced a more profound reduction in the size of the contractions than the same dose, or even double the dose, given one hour after the anaesthesia had been discontinued. Cyclopropane and chloroform on the other hand increased the response of the muscle to stimulation of the nerve, even during deep anaesthesia, but again the effect of curare was more marked during than after anaesthesia. Anaesthesia with "fluothane" (halothane) had little effect on the size of the muscular response, but once more curare had a more marked effect during than after administration of the anaesthetic.

Since ether was the only anaesthetic agent tested that had any depressant effect on the response of voluntary muscle to indirect stimulation, it is suggested that the muscular relaxation produced by the other agents is probably due to a central rather than to a peripheral action. No conclusions can be drawn from these experiments concerning the mechanism whereby all four agents potentiate the effect of curare. *W. Stanley Sykes*

1287. **Apneic and Hypotensive Effects of Local Anesthetic Drugs in Dogs and Mice under General Anesthesia**
L. A. WOODS and J. HAGGART. *Anesthesiology* [*Anesthesiology*] **18**, 831–840, Nov.–Dec., 1957. 20 refs.

During studies at the University of Michigan Medical School, Ann Arbor, of the tissue distribution of cocaine it was observed that anaesthetized dogs were less tolerant of the drug when injected intravenously than were unanaesthetized animals, death occurring from respiratory failure accompanied by hypotension. In a further investigation of the effect of local analgesics in inducing apnoea and hypotension in animals under general anaesthesia the LD_{50} values for cocaine, procaine, lidocaine, (lignocaine), and pentylenetetrazol, given intravenously, were determined in unanaesthetized mice and in mice anaesthetized with ether, chloroform, thiopentone, or pentobarbitone. (Pentylenetetrazol was included as a convulsant agent without local analgesic activity.) Similar estimations were carried out in dogs under ether anaesthesia.

In mice anaesthesia with ether and chloroform increased considerably the toxicity of all the agents tested, death being due to respiratory failure. Pentobarbitone and thiopentone anaesthesia on the other hand did not alter the toxicity of cocaine or lignocaine, and reduced that of procaine and pentylenetetrazol. In dogs deeply anaesthetized with ether apnoea was produced by cocaine, procaine, and lignocaine given intravenously in doses which had little or no effect on unanaesthetized animals. Attempts to antagonize the apnoea with nikethamide, pentylenetetrazol, and forced inspiration of carbon dioxide were unsuccessful, but spontaneous respiration was re-established on withdrawal of the ether. The apnoea was accompanied by hypotension, which persisted for several hours if artificial respiration was maintained. *W. Stanley Sykes*

1288. **The Current Status of the Tranquillizing Drugs.** [Review Article]
P. L. KURTZ. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **78**, 209–215, Feb. 1, 1958. Bibliography.

Chemotherapy

1289. ***In-vitro* Activity of Sigmamycin (a Combination of Tetracycline and Oleandomycin)**
R. W. FAIRBROTHER and J. E. SOUTHALL. *Lancet* [*Lancet*] **2**, 974–976, Nov. 16, 1957. 7 refs.

The studies here reported from Manchester Royal Infirmary into the activity of "sigmamycin", a combination of tetracycline and oleandomycin in the ratio of 2:1, against 165 common pathogens *in vitro* do not support the claim that these drugs act synergically. Indications of synergism of doubtful significance were observed only against very sensitive organisms. Such activity, if confirmed, would be unlikely to be of practical value, since infections with sensitive organisms can be dealt with adequately by a single antibiotic.

Support was, however, obtained for the contention that sigmamycin delays the emergence *in vitro* of resistant variants of *Staphylococcus aureus*, but as it cannot be assumed that similar results would follow the clinical application of the mixture, the practical value of this finding is uncertain. *L. A. Elson*

1290. **An Antibiotic from Maggots**
E. R. PAVILLARD and E. A. WRIGHT. *Nature* [*Nature* (*Lond.*)] **180**, 916–917, Nov. 2, 1957. 2 figs., 4 refs.

Experiments were carried out at St. Mary's Hospital Medical School, London, to determine whether an antibacterial agent having the properties of a true antibiotic was responsible for some of the beneficial effects of maggot therapy. Young larvae of the blow-fly, *Phormia terraenovae*, were sprayed with water at intervals for 3 hours and the washings sterilized by heat. The excreta in this suspension were bactericidal at 150 μg. per ml. against Group-A haemolytic streptococci and at 30 μg. per ml. against the pneumococcus. *Staphylococcus pyogenes* and *Clostridium welchii* were less sensitive and *Escherichia coli*, *Bacillus subtilis*, *Proteus vulgaris*, and *Candida albicans* highly resistant. By paper chromatography the active factor was located with an R_F value of 0·63, and relatively pure samples of this fraction were obtained. Daily injections of 25 to 50 mg. of this preparation protected mice against the lethal effects of intraperitoneal inoculation with Type-1 pneumococci. *V. J. Woolley*

1291. **The Effect of Various Drugs on the Growth of *Candida albicans* during Antibiotic Therapy, Including Amphotericin, a New Antifungal Antibiotic**
A. J. CHILDS. *Scottish Medical Journal* [*Scot. med. J.*] **2**, 400–402, Oct., 1957. 6 refs.

Following the author's earlier observation (*Brit. med. J.*, 1956, **1**, 660; *Abstr. Wld Med.*, 1956, **20**, 258) that nystatin had some limited effect in inhibiting the increased growth of *Candida albicans* which may occur in patients undergoing treatment with antibiotics, the effects of three new drugs, amphotericin, chlorohydroxyquinoline, and chlorohydroxyquinoldine, on the growth of this fungus were investigated. Each drug was given orally to a group of male patients over 12 years of age being treated with tetracycline at Ruchill Hospital, Glasgow, for pneumonia, one group receiving nystatin alone and another (control) group tetracycline alone. The number of patients in each group ranged from 25 to 33 and all the drugs were given for 5 days. Specimens of sputum and rectal and throat swabs were taken before treatment and again on the 3rd, 5th, 7th, and 9th days in hospital.

Before treatment *C. albicans* was present in 17% of rectal swabs, 25% of throat swabs, and 42% of sputa. The organism was present in 17, 46, 67, and 53% of rectal swabs on the 3rd, 5th, 7th, and 9th days respectively after treatment with tetracycline alone. In the other groups the number of specimens from which *C. albicans* could be isolated fell progressively, although there was a slight rise on the 9th day in the number of specimens from those treated with nystatin and chlorohydroxyquinoline. The incidence of isolation of *C. albicans* from throat swabs increased in all groups during treatment, although the increase was somewhat less in the nystatin- and amphotericin-treated groups. The incidence of the fungus in the sputum also increased in all groups. The author concludes that whereas all these three drugs and nystatin reduced the population of yeasts in the intestine, only a slight effect was produced on the throat flora by nystatin and amphotericin, and these two had little or no effect on the sputum. *R. F. Jennison*

1292. **The Tuberculostatic Activity of a Structural Analogue of Isoniazid, *iso*Nicotinyl-1-amino-2:5-dimethylpyrrol (G. 144).** (Activité tuberculostatique d'un analogue structural de l'isoniazide: l'isonicotinylamino-1-dimethyl-2: 5-pyrrol (G. 144))
J. M. GAZAVE, N. P. BUU-HOÏ, and N. D. XUONG. *Thérapie* [*Thérapie*] **12**, 486–492, 1957. 1 fig., 11 refs.

The authors, who have previously reported that haemin reduces the tuberculostatic activity of hydrazides, such as isoniazid, but not of hydrazide-free drugs, such as 4-ethyl-4-*iso*amyloxythiocarbanilide (*C. R. Acad. Sci.* (*Paris*), 1955, **241**, 1525), have now examined, at the Radium Institute and the Rothschild Hospital, Paris, the tuberculostatic activity *in vitro* of a hydrazide-free analogue of isoniazid, *iso*nicotinyl-1-amino-2:5-dimethylpyrrol (G. 144). This substance is insoluble in water, but soluble in lipids and in organic solvents such as alcohol, glycerol, and diethylene glycol. In this preliminary report it is shown that the tuberculostatic activity of G. 144 in a concentration of 0·62 μg. per ml. is only slightly less than that of isoniazid, but that its oral toxicity for mice (LD_{50} 555 mg. per kg. body weight) is less than one-third that of isoniazid. It is suggested that G. 144 could be administered in smaller doses and at greater intervals than isoniazid. *J. E. Page*

Infectious Diseases

1293. **Emergency Treatment of Respiratory Failure in Poliomyelitis**
H. B. C. SANDIFORD. *Lancet* [*Lancet*] **2**, 823–825, Oct. 26, 1957. 4 refs.

The author, in this paper from the Infectious Diseases Hospital, Portsmouth, emphasizes the importance of careful planning of the transport of patients with respiratory failure in poliomyelitis. He describes 5 cases illustrating the value of skilled supervision of the removal of such patients. A well trained team, with an anaesthetist in command, should always be available when patients have to be moved from one hospital to another and should be prepared to go to a hospital at the periphery to help in the management of difficult cases.
John Fry

1294. **Epidemic Salmonellosis. A 30-month Study of 80 Cases of *Salmonella oranienburg* Infection**
V. L. SZANTON. *Pediatrics* [*Pediatrics*] **20**, 794–808, Nov., 1957. 3 figs., 12 refs.

This paper from the Griffin Hospital, Derby, Connecticut, describes a 30-month study of an epidemic of salmonellosis in which 46 newborn infants in the obstetric department were affected and 34 older contacts became carriers. In all cases stool cultures were positive for *Salmonella oranienburg*. The 46 affected infants constituted about 20% of the infants delivered at the hospital during the period. The exact mode of spread of the infection could not be accurately determined. Of the babies, one died, 7 were very ill, 33 had abnormal stools only, and 5 were asymptomatic. Of the infected contacts, all but one were free from clinical symptoms. Antibodies against *Salm. oranienburg* were detected in the serum of 9 of the 10 infants and 7 of the 8 carriers studied. Of 33 infants from whom repeated stool cultures could be made over an adequate period, all became carriers—that is, the cultures remained positive 10 or more days after the cessation of symptoms or in the absence of illness. However, in all but 3 of these the stools had become negative on culture by the end of the survey.

Treatment with various antibiotics was tried, but had no curative effect on the carrier state. Indeed, a comparison suggested that the stools of an untreated group cleared spontaneously more rapidly than those of the treated group.
Winston Turner

1295. **A Family Outbreak of Histoplasmosis. I. Clinical, Laboratory, and Follow-up Studies**
K. P. KOLB and C. C. CAMPBELL. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **50**, 831–840, Dec., 1957. 5 figs., 13 refs.

An account is given of an epidemic of histoplasmosis which occurred within 5 miles of the city limits of Washington, D.C., affecting all 4 members of a family—a man, his wife, his son, and his sister-in-law—the onset in all 4 cases occurring within the same week. The man was critically ill for 2 months, but in the other 3 cases the symptoms were less severe. *Histoplasma capsulatum* was isolated from the sputum in the first 2 cases and significant levels of antibodies to the organism in the serum and skin reactions to histoplasmin were demonstrated in all 4.

The man, aged 33, gave a history of 10 days' fever, nausea, vomiting, diarrhoea, headache, and general malaise. This was followed by chills and pain over the right side of the chest which was worse on deep breathing. On admission to hospital there were scattered rales throughout both lung fields, the temperature was 103° F. (39·4° C.), and the leucocyte count 5,900 per c.mm., of which 50% were polymorphonuclear granulocytes. Radiographs of the chest showed nodular and circumscribed soft infiltrations diffusely scattered over both lung fields in miliary fashion. Treatment with oxytetracycline and with streptomycin and PAS had little effect on the fever, but chloramphenicol, substituted for the oxytetracycline, appeared to bring the temperature down to 100° F. (37·8° C.). However, on withdrawing chloramphenicol after 3 weeks the temperature rose again and no longer responded to this drug. Penicillin had little effect. After isoniazid had been substituted for streptomycin and PAS the temperature gradually fell to normal. The other 3 cases ran a comparatively short course.

Of particular interest is the radiological picture five years later. In the radiographs of the man and his wife there was no calcification and no appreciable change in nodular density, whereas in those of the son there was a "snow-storm" pattern of calcification. Strongly positive skin reactions to histoplasmin persisted in all the patients.
Kenneth M. A. Perry

1296. **A Family Outbreak of Histoplasmosis. II. Epidemiologic Studies**
C. C. CAMPBELL. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **50**, 841–848, Dec., 1957. 26 refs.

Epidemiological investigation of the family outbreak of histoplasmosis described in the previous paper [see Abstract 1295] revealed a number of possible sources of infection with *Histoplasma capsulatum*. These included decaying wood, birds, their nests and eggs, rodents, and domestic pets. The man and his son had together collected chicken compost from the floor of an old chicken coop on a nearby farm for use as manure in their garden 10 days before the onset of their illness, while his wife and sister-in-law had worked in this garden during the next few days. *Histoplasma capsulatum* was isolated from the floor of the chicken coop 4½ years after the primary infections. The occur-

rence of these cases indicates that the District of Columbia is an area of high endemicity for histoplasmosis. It also draws attention to the fact that in communities in which gardening is a common pursuit the transport of infected compost in cars or trucks may result in the widespread distribution of spores.

Kenneth M. A. Perry

1297. **Experiences with the Therapy of Sixty Cases of Deep Mycotic Infections**

P. H. LEHAN, J. L. YATES, C. A. BRASHER, H. W. LARSH, and M. L. FURCOLOW. *Diseases of the Chest* [*Dis. Chest*] **32**, 597–614, Dec., 1957. 8 figs., 28 refs.

A new antibiotic, amphotericin B, derived from a soil *Streptomyces*, was tried in the treatment of 19 cases of mycotic infection, the daily dosage being up to 8 g. by mouth or 1 mg. per kg. body weight intravenously. Of 6 patients with *Cryptococcus neoformans* meningitis 2 died (oral administration in one and intravenous in one), 3 (oral administration in one) made a good recovery, remaining asymptomatic for 4 to 12 months, while in one (intravenous injection) recovery was only fair. There were 6 patients with progressive disseminated histoplasmosis; 2 treated orally showed temporary improvement (one died later) and of 4 given the drug intravenously, 2 died and 2 made a good recovery. In 6 cases of chronic progressive pulmonary histoplasmosis oral administration of amphotericin B resulted in one good and one fair response, and intravenous injection in 2 good and 2 moderately good responses. A good clinical response was obtained in one patient with severe acute pulmonary histoplasmosis given the drug intravenously.

There were no toxic effects with oral administration, but minor gastro-intestinal symptoms and headache were observed in several cases following intravenous injection. In one there was a transient rise in the blood urea level.

Gerald Sandler

1298. **The Effective Use of Piperazine for the Treatment of Human Helminthiases**

C. SWARTZWELDER, J. H. MILLER, and R. W. SAPPENFIELD. *Gastroenterology* [*Gastroenterology*] **33**, 87–96, July, 1957. 12 refs.

Writing from Louisiana State University School of Medicine, New Orleans, the authors review the results obtained with various salts of piperazine in the treatment of enterobiasis, uncomplicated ascariasis, and partial intestinal obstruction due to infection with *Ascaris lumbricoides*.

In enterobiasis diagnosis was made by the identification of eggs of *Enterobius vermicularis* on anal swabs and the efficacy of the drug was evaluated by examination of 7 post-treatment swabs within 2 weeks of completion of therapy, complete absence of eggs on all 7 swabs being the criterion of cure. The drug employed was piperazine citrate given as a syrup in a dose of 30 to 35 mg. per lb. (66 to 77 mg. per kg.) body weight per day to a maximum daily dose of 2 g. The 82 patients were divided into three treatment groups. Those receiving Regimens A and B were given daily treatment for 2 weeks in alternate weeks and consecutive weeks respectively; in both these groups the daily total was divided into 2 equal doses. In Regimen C the drug was given as a single dose daily for 6 consecutive days. Regimen A cured 26 of 27 patients treated, Regimen B cured 30 of 33 cases, and Regimen C cured 21 of 22 cases. There was thus no significant difference in efficacy between the three methods of treatment. A few of the patients vomited or complained of mild abdominal cramps, but no serious side-effects were observed. It is concluded that the 6-day course of therapy with a single daily dose of piperazine citrate is as effective as more protracted courses.

In uncomplicated cases of ascariasis the diagnosis was made by the presence of the eggs of *A. lumbricoides* in formalin–ether stool concentrates and the criterion of cure was the absence of eggs in such a concentrate one week after treatment. Of the 60 patients treated, 30 were given piperazine citrate, 15 piperazine adipate, and 15 piperazine phosphate in single weekly doses of 70 mg. per lb. (154 mg. per kg.), with a maximum dose of 3 g. Except for one defection, all the patients received 2 weeks' treatment. One week after the first dose the cure rates were as follows: with piperazine citrate 25 out of 30 (83%), with piperazine adipate 10 out of 15 (67%), and with piperazine phosphate 12 out of 15 (80%). After 2 weeks' treatment the corresponding cure rates were 97, 100, and 93% respectively. No intolerance to the treatment was encountered. It is concluded that for all practical purposes the three piperazine salts were equally efficacious and that no fasting or purgation is required.

In the third study 7 children under 4½ years of age suffering from partial intestinal obstruction due to ascariasis were treated with piperazine citrate syrup, either in a dose of 35 mg. per lb. (77 mg. per kg.) twice a day for 6 doses or in a single dose of 70 mg. per lb.(repeated once when necessary). Supportive therapy included abdominal decompression by Levin tube in 3 cases, repeated enemata in 5 cases, and parenteral administration of fluids in 4 cases; surgical intervention was not required. Large numbers of worms were passed 2 to 5 days after treatment began, and 6 of the 7 patients were discharged after 6 days in hospital. The authors emphasize that piperazine citrate syrup is a safe and effective anthelminthic for the treatment of this complication of ascariasis, and that administration of the drug by intubation as early as practicable following abdominal decompression represents an important part of the treatment. The use of saline enemata is also of considerable value as part of the management of this complication. An outline of recommended treatment is included [and should be read in detail in the original]. The authors make it clear that these recommendations refer to cases of partial intestinal occlusion and not complete stoppage.

O. D. Standen

1299. **Encephalomyelitis in North West London. An Endemic Infection Simulating Poliomyelitis and Hysteria**

A. M. RAMSAY. *Lancet* [*Lancet*] **2**, 1196–1200, Dec. 14, 1957. 3 figs., 11 refs.

Tuberculosis

DIAGNOSIS AND PROPHYLAXIS

1300. **Enhancement of Mantoux Reaction Coincident with Treatment with Cortisone and Prednisolone**
L. H. TRUELOVE. *British Medical Journal* [*Brit. med. J.*] 2, 1135–1137, Nov. 16, 1957. 20 refs.

Following the observation that a patient with Addison's disease had initially a negative Mantoux reaction at a dilution of 1 in 100 but that this reaction had become positive at a dilution of 1 in 1,000 37 days later while she was receiving a daily maintenance dose of 50 mg. of cortisone, the author carried out Mantoux tests on all (24) patients admitted with a variety of disorders to Stoke Mandeville Hospital, Aylesbury, Bucks, who were likely to need corticosteroid therapy and who were Mantoux-negative on admission (at a dilution of 1 in 100 in 13 cases and of 1 in 1,000 in 11 cases). They comprised 14 men and 10 women ranging in age from 24 to 80, the majority being over 60.

In addition to receiving the treatment appropriate to their particular ailment these patients were given either cortisone in doses ranging from 25 to 75 mg. daily or prednisolone, 15 to 60 mg. daily. Of the 24 patients 20 subsequently showed a positive Mantoux reaction, 3 of them who had previously been negative at a dilution of 1 in 100 becoming positive at 1 in 1,000. In the majority of the cases the time interval between the two tests was less than 2 weeks. The clinical course of their disease seemed to have no bearing on the reversion to a Mantoux-positive reaction; thus 6 of those who reverted showed marked improvement, 6 showed no change, 3 deteriorated and subsequently died, while 3 were not very ill at any time.

A further case, that of a man of 35 with pneumonia and pleural effusion, is recorded in some detail, in which the Mantoux reaction became positive following recovery of adrenocortical function which had been depressed during the acute stage of the illness, no steroid drugs having been administered. The suggestion is made that although steroid treatment is able to suppress a positive tuberculin reaction when given in high dosage, it may, when given in lower dosage, actually restore a reaction which has been suppressed by age, infection, or adrenal deficiency. *H. F. Reichenfeld*

1301. **Assessment of BCG Vaccination in India. Second Report**
WHO TUBERCULOSIS RESEARCH OFFICE. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] 17, 203–224, 1957. 6 figs., 10 refs.

From the first report of the World Health Organization regional team for the assessment of mass B.C.G. vaccination in India, which was issued in 1955 (*Bull. Wld Hlth Org.*, **12**, 101) two important points emerged: (1) the level of post-vaccination allergy was variable and sometimes very low; and (2) non-specific tuberculin sensitivity was widespread and varied in different geographic areas. Accordingly the team made a second visit to India—the subject of this report—from February to June, 1955, in order to confirm these findings and to investigate some of the problems they raised. Three main studies were carried out. The first was on 24 groups of B.C.G.-vaccinated school-children (total number 1,532) who had been tuberculin tested by the team in 1954 and were retested in 1955; these groups contained some of the highest and lowest levels of allergy found at the first post-vaccination testing. In addition, there were 16 groups of school-children and of the general population (total number 1,343) who had been vaccinated in the previous 10 months but who had not been tested for post-vaccination tuberculin allergy. The second study, an investigation of the vaccination technique and potency of the Madras (mass-campaign) vaccine, was performed at 28 schools in an attempt to identify factors responsible for the variable results found in previous mass vaccination. In the third study the problem and prevalence of non-specific, naturally acquired tuberculin sensitivity was investigated in seven unvaccinated village populations in Mysore and Madras adjacent to areas where the greatest frequency of non-specific sensitivity had been found in the first survey. The techniques employed were identical with those used in the 1954 survey. The intradermal test with 5 t.u. (0·0001 mg.) of tuberculin was used for all groups, 0·1 ml. of P.P.D. (prepared by the State Serum Institute, Copenhagen) being injected into the dorsal forearm surface and read after 3 to 4 days by measuring the diameter of the area of induration. No attempt was made to classify reactions as " positive " or " negative ", the criterion for vaccination being an area of induration of 9 mm. or less in diameter on challenge with 5 t.u. Precautions were taken to preserve statistical validity of comparisons in all observations.

The results of retesting the school-children in the first study showed that the level of allergy (expressed as diameter of the induration) was higher in 1955 than in 1954, the mean reaction size for all persons tested in 1955 being 13·1 mm., whereas in 1954 it was 11·3 mm.; further, the mean reaction size in children tested for the second time in 1955 was 13·4 mm., compared with 11·4 mm. in children tested for the first time in 1955. The latter finding is consistent with the concept that repeated tuberculin testing may itself preserve or increase allergy induced by B.C.G. vaccination, but from the fact that there was much less variation in reaction size in the 1955 survey compared with that of 1954 (in addition to the special precautions taken to prevent deterioration of tuberculin potency in 1955) it is concluded that instability of the tuberculin was responsible for the lowest results recorded in 1954 rather than any defect in the vaccine or the vaccination technique. In the 16 additional groups of children and of the general population the findings were similar.

In the studies of vaccination technique comparison of the results of the mass campaign field procedures with

those of the assessment team showed that the levels of allergy production were not significantly different. It was concluded that the only factor clearly reducing the production of allergy was prolonged storage of vaccine. It was shown that the mean size of post-vaccination tuberculin reactions fell by more than 1 mm. for every 2 weeks of storage. Vaccinated children did not attain a degree of allergy as great as that induced by natural tuberculous infection, but allergy produced by the freshest vaccine was " nearly as strong " and that produced by vaccine stored for 4 weeks or less was considered to be satisfactory.

In the third study the tuberculin testing of 2,615 unvaccinated villagers was carried out in the low-lying and humid regions adjacent to Travancore–Cochin, where in 1954 such a high frequency of non-specific tuberculin sensitivity was found that the 5-t.u. test was almost valueless in separating infected from uninfected children. The studies in 1955 confirmed these findings. It is suggested that the widespread prevalence of non-specific reactions virtually destroyed the value of the test in these areas, and probably also that of any other tuberculin tests in use today. A similar situation exists in Burma, the Phillipines, the Sudan, Nigeria, and some other tropical areas and seriously interferes with tuberculosis control programmes. Some evidence was obtained, however, that by increasing the volume of the tuberculin diluent a slightly better separation of infected from uninfected subjects can be achieved, but further investigation is required. The authors conclude that a more specific tuberculin test is the most rational solution to the problem, and work is now in progress to attempt fractionation of the various tuberculin components.

Raymond Parkes

1302. **Interpretation of Tuberculin Reactions in Populations with a High Proportion of BCG-vaccinated Persons**
J. GULD. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **17**, 225–248, 1957. 4 figs., 18 refs.

Tuberculin testing has been used extensively at the Central Tuberculosis Dispensary, Copenhagen, to identify cases of recently developed tuberculous infection. As some known tuberculin-positive individuals were found to be tuberculin-negative on retesting—an inconsistency which has increased in frequency at the Dispensary in the last few years—the present investigation was carried out to establish the cause of such conflicting results.

The routine tuberculin test employed consisted in giving an intradermal injection of 3 tuberculin units (t.u.), followed by a second injection of 10 t.u. if the first provoked no reaction. Reactions were recorded 3 or 4 days later by measuring the diameter of the area of induration, and if this was 10 mm. or greater the result was recorded as positive. In addition, the investigation was extended to determine (1) whether a single test with 5 t.u. could be substituted for the two-dose method; (2) with what consistency the size of the tuberculin reaction was measured by different observers; and (3) whether repeated yearly testing always at the same site on the arm might influence the response to the test. All tests and readings were carried out by trained nurses with long experience of this work.

Nearly 1,000 non-tuberculous persons, the majority of whom were adults, were included in the main study, and one or other of two testing procedures was employed: (1) the intradermal injection of 3 t.u. followed by 10 t.u. if the first injection produced a reaction of 13 mm. or less after 3 days; (2) an injection of 5 t.u. which, if causing a reaction of 15 mm. or less 3 days later, was repeated. Reactions in the group of non-tuberculous persons studied were compared with those in similarly tested groups of persons (in roughly comparable numbers) previously vaccinated with B.C.G. [presumably tested concurrently]. Among the unvaccinated subjects two peaks of reaction size occurred in response to the test, both with 3 t.u. and with 5 t.u., one at a diameter of 2 to 4 mm. and the other at 16 to 18 mm. which, the author states, " is the characteristic average for infected persons ". But in the B.C.G.-vaccinated persons the distribution of reaction sizes was quite different, the single peak, or rather plateau, being predominantly between 10 and 17 mm. The mean reaction to 5 t.u. was slightly larger than that to 3 t.u. Individuals whose reactions to 3 t.u. were 13 mm. or less and who received a second test with 10 t.u. showed similar reaction patterns, confirming the impression that " there are two kinds of non-vaccinated people but only one kind of B.C.G.-vaccinated ". The unvaccinated group included some subjects who reacted no more strongly to 10 t.u. than to 3 t.u. and who appeared to be relatively insensitive to the tuberculin dose used; in contrast, all persons with reactions to 3 t.u. greater than 5 to 6 mm. showed still larger reactions to 10 t.u., appearing to be highly tuberculin-sensitive. By comparison, B.C.G.-vaccinated persons revealed a uniform sensitivity and almost all reacted more strongly to 10 than to 3 t.u. But although vaccinated subjects showed varying sensitivity, they did not, like the unvaccinated, fall into two distinct reacting groups, and analysis of the total results for this group suggested that they tended on the whole to exhibit " a somewhat weak sensitivity ". Again, comparison of these results with similar tests in the same persons over a previous 5-year period showed that the classification of the unvaccinated as " positive " or " negative " reactors was reproduced fairly constantly year by year, while the B.C.G.-vaccinated subjects showed considerable variability and inconstancy which might be due to " a low degree of allergy that may or may not be revealed by any single test ". Evidence was also adduced that a single test with 5 t.u. is an inaccurate measure of tuberculin sensitivity.

The classification of reaction size by different observers was found " reasonably consistent " in unvaccinated persons, but classification of the B.C.G.-vaccinated as negative or positive was quite impossible. In the latter group some observers reported no reaction in subjects in whom other observers had found reactions of 10 to 20 mm., which were soft and flat. As it is known that repeated use of the same skin site for intradermal testing causes reactions to later injections to reach maximum size sooner and disappear more quickly than those at a fresh site, the author suggests that the discrepancies may

be due to such " accelerated " reactions (and in fact B.C.G.-vaccinated persons at the Dispensary always received the injection at the same site). The validity of this suggestion was confirmed in 70 B.C.G.-vaccinated persons by comparing the reaction to a test with 3 t.u. given at the customary site with that on the opposite arm in each individual; this showed that the former appeared and vanished much more quickly. In conclusion attention is drawn to the fallacy of referring to persons as " tuberculin positive " or " tuberculin negative " in geographical areas (such as South East Asia) where non-specific sensitivity is common and strong, and also to the inaccuracies which may arise if too much reliance is placed on the comparison of the different quality and size of reactions in B.C.G.-vaccinated subjects with those following natural infection as a means of differentiating the two forms of sensitivity.

Raymond Parkes

1303. **Effect of Intradermal Tuberculin Tests on BCG-induced Allergy**

K. MAGNUS. *Bulletin of the World Health Organization [Bull. Wld Hlth Org.]* **17**, 249–254, 1957. 1 fig., 6 refs.

The first of the two experiments reported in this paper from the W.H.O. Tuberculosis Research Office, Copenhagen, was designed to determine whether waning B.C.G.-induced allergy is enhanced by further intradermal tuberculin tests. It was carried out on 40 guinea-pigs, all of which were tested with 5 t.u. of tuberculin 7 months after vaccination. To determine the effect of tuberculin testing during the preceding month on the result of the final test the animals were divided into two main groups (I and II), which were further divided at random into four subgroups. Subgroup (*a*) received four " interim " tuberculin tests, one every week, Subgroup (*b*) received only one at the beginning of the month and Subgroup (*c*) one towards the end, while Subgroup (*d*) had no interim test. The dose for each interim test in Group I was 5 t.u. and in Group II was 100 t.u., both being injected into the skin of the flank and no injection site being used more than once. Reactions were read after 24 hours and expressed as the average of the longitudinal and transverse diameters of induration. In Group I (5 t.u.) the average size of the reaction to the final test in the first 3 subgroups was 9 to 12 mm. compared with 6 mm. in the control subgroup, so that vaccination allergy was " clearly and consistently enhanced by injection of tuberculin ". In Group II (100 t.u.) the mean reaction size was slightly greater, but the difference from Group I was not statistically significant. Comparison of Subgroup (*a*) with Subgroups (*b*) and (*c*) showed that animals given four injections had " lower allergy " than those given only one injection. It is concluded that there is no clear relation between the dose of tuberculin and an increase in allergy, while repeated post-vaccination tests may cause the enhancing effect to be partly annulled by a desensitization effect.

In the second experiment, which was undertaken to determine (1) the duration of increased or sustained allergy due to post-vaccination tuberculin tests, and (2) whether the same effect could be obtained with another tuberculin product and in a dose less than 5 t.u., 44 B.C.G.-vaccinated guinea-pigs were divided at random into 16 test groups of 2 animals each, and 2 groups of 6 animals as controls. The 16 groups were given an interim injection of 1 or 5 t.u. of either P.P.D. or old tuberculin at an interval of 1, 2, 4, or 8 weeks before allergy was to be tested. To assess the degree of allergy a final test with 5 t.u. of the same type of tuberculin used for the interim injection was given, one control group being tested with P.P.D. and the other with old tuberculin in the same way. In all the groups receiving interim tests, other than that given 1 t.u. of P.P.D., allergy was significantly higher than in the controls. The effect of the tuberculin injection decreased with time, but was still present after 8 weeks. There was no demonstrable difference between the effects of 1 t.u. and 5 t.u. of old tuberculin, but old tuberculin produced a larger final reaction than did P.P.D. However, because of a difference in the potency of the two dilutions it could not be concluded that the allergy-increasing effect of old tuberculin is greater than that of P.P.D. It is not known whether enhancement of tuberculin allergy by tuberculin injection can be evoked in guinea-pigs infected with living tubercle bacilli as it is in those vaccinated with B.C.G. Finally, the author points out that the problem whether tuberculin-induced variations in B.C.G. allergy are associated with changes in immunity remains to be investigated.

Raymond Parkes

1304. **Comparative Study of Heaf Tuberculin Tests with PPD and Freeze-dried BCG Vaccine**

J. E. HENSHAW. *Tubercle [Tubercle (Lond.)]* **38**, 411–415, Dec., 1957. 5 refs.

Writing from the Tuberculosis Unit, Port Harcourt, Nigeria, the author states that not less than 200,000 tuberculin tests have been carried out in that country by the Heaf multiple-puncture method. The use of B.C.G. for skin testing has been recommended by various authors, and its substitution for tuberculin in tests carried out as part of a B.C.G. vaccination programme was suggested by Heaf in 1955. In the present paper a comparative investigation of " bacillary " and " tuberculin " allergy with the multiple-puncture test is reported.

The author used freeze-dried vaccine from the Pasteur Institute in Paris, diluting it to various strengths with sterile distilled water instead of the special diluent provided. Tests with B.C.G. suspension and the purified protein derivative (P.P.D.) of tuberculin were performed simultaneously, one on each forearm. A different Heaf apparatus was used for each strength of B.C.G. and for each new group tested with P.P.D. The results were read independently at 72 hours by the author and a health visitor, each seeing only one arm and being unaware of the result recorded by the other. The degree of reaction was estimated according to defined criteria. During a survey 1,228 unvaccinated individuals between the approximate ages of 10 and 40 years were tested with P.P.D. (2 mg. per ml. with 10% glycerol) and with B.C.G. suspension containing 1, 3, 6, 12, 18, 24, or 30 mg. per ml. In addition, tests were carried out on 149 leprous patients (with 6 to 18 mg. of B.C.G. per ml.) and on 48 tuberculous patients (with 6 mg. of B.C.G. per ml.).

The results, which are set out in two tables, indicate that the Heaf test with suspensions containing 6 mg. of B.C.G. or more per ml. will indicate tuberculous infection in a higher proportion of individuals than the same test with P.P.D. in the strength used. The author's findings lend support to the view that there may be two types of allergic response to infection with the tubercle bacillus—" total allergy " elicited by the whole bacillary body and " fractional allergy " elicited by the protein fraction, and it is suggested that the use of the B.C.G. test may help in the investigation of so-called " non-specific " tuberculin sensitivity, which may be due to sensitization to a protein antigenically related to one of those of *Mycobacterium tuberculosis*. It also has the advantage that the reaction fades more slowly than that to P.P.D. The B.C.G. test by the multiple-puncture method, for which less skilful operators are required and exact measurement of the reaction is unnecessary, is recommended for use in tuberculin surveys preceding B.C.G. vaccination as being a more sensitive indicator of tuberculous infection than the standard test with P.P.D.

Norman F. Smith

RESPIRATORY TUBERCULOSIS

1305. **Prednisolone in the Treatment of Pulmonary Tuberculosis: a Controlled Trial**

A Preliminary Report by the Research Committee of the Tuberculosis Society of Scotland. *British Medical Journal* [*Brit. med. J.*] **2**, 1131–1134, Nov. 16, 1957. 2 figs., 9 refs.

This paper is a preliminary report of a 6-month controlled trial, carried out at seven Scottish centres, of the effect of adding a corticosteroid (prednisolone) to the usual chemotherapy in the treatment of pulmonary tuberculosis. It deals with 90 of the first 110 patients completing 6 months' treatment, of whom 46 were in the control group and 44 in the " steroid group ". The two groups were closely matched in respect of age and sex, all patients were in hospital for 6 months, being confined to bed for the first 3 months, and both groups received identical courses of chemotherapy, which are described in detail. The steroid group received in addition, during the first 3 months of the investigation, prednisolone in a dosage of 5 mg. four times daily, plus ACTH-gel, 30 units intramuscularly on two successive days every fortnight, plus 2 g. of potassium citrate twice daily. The patients' ages ranged from 15 to 64, and 54% were male and 46% female. In regard to the type of tuberculosis, 93·2% of the patients in the steroid group were suffering from the acute form of the disease compared with 78·3% in the control group, the balance in each case being made up of patients with a recent flare-up of chronic disease. The two groups were comparable in respect of extent of the disease, four-fifths of the patients in both groups having at least three zones involved. The number of cavities present in each group was 50, while the sputum was positive for tubercle bacilli in 98% of the controls and 88% of the steroid group.

In general, the clinical condition of patients in the steroid group improved more rapidly than of those in the control group in respect of subsidence of fever, improvement in appetite, weight gain, and lowering of the erythrocyte sedimentation rate. Radiological improvement was also on the whole more rapid in the steroid group, the trend being statistically significant throughout the 6 months, although a highly significant difference in favour of the steroid group was observed only at the second month. Moderate or slight radiological deterioration occurred in 7 patients in the steroid group between the third and fourth months, that is, just after the withdrawal of steroid therapy, but this " rebound phenomenon " was not apparent from the statistical analysis; all but one of these patients subsequently improved. At the end of the 6 months 85% of cavities in the steroid group and 72% of those in the control group had closed. As the authors point out, while this difference is not statistically significant, the practical significance of the finding and the higher rate of closure in the steroid group cannot be discounted at this early stage of the trial. All 83 sputum-positive patients had become sputum-negative at the end of the 6 months, the rate of conversion being slightly higher in the steroid group throughout the period, though not significantly so. Toxic effects from chemotherapy were noted in a few patients in each group, vestibular dysfunction due to streptomycin occurring in 4 cases in the control group and in 2 in the steroid group. Among the side-effects of prednisolone were moon-face in 46% of cases and a skin rash which appeared on cessation of steroid therapy in 17 cases, in 11 of them within 2 weeks of withdrawal of the drug. In 18 cases the diastolic blood pressure persistently exceeded 100 mm. Hg during prednisolone therapy, chiefly in the last 6 weeks of treatment; in 2 cases an early rise in this pressure to 115 and 140 mm. Hg respectively led to withdrawal of the drug.

In discussing these preliminary results the authors point out that the present investigation has demonstrated the value and safety of corticosteroid therapy for patients with active pulmonary tuberculosis, provided there is adequate chemotherapeutic cover, and suggest that the use of these steroids may also be warranted in acutely ill patients when the rapid abatement of severe symptoms is desirable.

H. F. Reichenfeld

1306. **The Ambulatory Treatment of Patients Hospitalized with Pulmonary Tuberculosis**

J. A. Wier, R. L. Taylor, and R. S. Fraser. *Annals of Internal Medicine* [*Ann. intern. Med.*] **47**, 762–773, Oct., 1957. 13 refs.

This study, reported from Fitzsimons Army Hospital, Denver, Colorado, was designed to evaluate the importance of rest in bed during the chemotherapy of pulmonary tuberculosis, and was carried out on 108 patients with minimal lesions, an unspecified number with pleural effusion, and 203 with moderately or far-advanced lesions; seriously ill patients with persistent pyrexia were excluded from the study. The patients with each type of disease were divided at random into two groups, one being treated with the regimen of modified bed rest used in the hospital and the other allowed from the outset to get out of bed, with freedom of the ward and

its immediate vicinity, participation in occupational therapy, non-strenuous games, and tidying of their bed-spaces, being allowed to rest on their beds if they wished, though they were not encouraged to do so.

All patients with minimal lesions and pleural effusions in both groups did well, so that comparison in respect of these cases was not possible. Of the 203 patients with advanced or moderately advanced disease, 95 were kept in bed and 108 were ambulatory, the proportions of far-advanced cases in the two groups being 22 and 38% respectively and the corresponding proportions of cases with cavities being 73 and 84% respectively. Symptomatic improvement occurred with about equal frequency. Radiological progress was assessed at 120, 180, and 240 days, and on each occasion the ambulatory group was found to have done slightly better than the resting group [though the statistical significance of the difference between the groups was not determined and on inspection appears not to be marked]. Equally good results were obtained in both groups in respect of sputum conversion and weight gain. As a result of this study the regimen of bed rest hitherto in force has been relaxed and the authors point out the advantages to the hospital and to the patient—to the former in the lesser demands on the nursing staff, and to the latter in making it possible to organize ambitious training programmes of both an academic and vocational nature.

H. F. Reichenfeld

1307. **The Place of Drug Therapy in the Management of Unhospitalized Tuberculosis Patients**
A. B. Robins and A. D. Chaves. *Annals of Internal Medicine* [*Ann. intern. Med.*] **47**, 774–781, Oct., 1957. 3 refs.

Antimicrobial therapy with combinations of isoniazid, streptomycin and PAS has been studied over a 2-year period in 1,631 patients with active pulmonary tuberculosis started on treatment in the 23 chest clinics of the New York City Department of Health between July 1, 1953, and June 30, 1954. The majority of the 831 patients observed for the full 2 years were older males with advanced disease of long standing and histories of previous unsuccessful hospital treatment.

Sputum conversion occurred in 62% of the patients whose sputum was positive on culture before treatment. Roentgenographic improvement was noted in 50%. The classification of "arrested" was made in 455, and "arrested with residual cavitation" in an additional 87 patients; 65% of all patients had reached a stage of clinical stability by the end of the 24 months. If allowance is made for patients discontinued from supervision after more than 6 and less than 18 months of treatment, reversal of infectiousness occurred in 49% and arrest of the disease in 51% of all patients treated. Unfavourable *x*-ray changes took place in 11% of the patients. In no instance were tubercle bacilli recovered at the end of 2 years from a patient whose sputum before drug treatment was negative.

This study has provided no evidence that the provision of drugs by the chest clinics of the New York City Health Department has contributed to the development of resistance to isoniazid in a significant number of patients, or unfavorably affected the acceptance of hospitalization by the tuberculous. It is the firm conviction of the writers that a program of antimicrobial therapy in clinics is an essential supplement to the hospital treatment of patients with active pulmonary tuberculosis.—[Authors' summary.]

1308. **Late Relapse in Primary Tuberculosis of the Lung with Segmental Infiltration.** (Die späten Rezidive bei den segmentalen Infiltrierungen der Primärtuberkulose)
A. F. Riebel. *Tuberkulosearzt* [*Tuberk.-Arzt*] **11**, 745–750, Dec., 1957. 3 figs.

In an investigation of [32 cases of] late relapse after primary tuberculous segmental infiltration of the lung it was found that local recurrence accounted for 9·3% and haematogenous dissemination for 28·9%, while bronchogenic spread to adjoining segments had occurred in 38·2% and to distant segments in 23·6% of cases. The latent interval was longest in the cases of haematogenous dissemination, which occurred almost exclusively at puberty. The delay was also long in cases of bronchogenic spread to distant segments, and was relatively short (mean 3·9 years) only in cases of bronchogenic spread to adjoining segments. Among boys spread occurred with equal frequency in all age groups; among girls the incidence of spread increased nearly fivefold between the age of 6 and puberty. Direction of spread showed no uniformity, any lobe and either side being liable to be involved. There appear to be no effective means of prophylaxis. From the point of view of prognosis, reactivation remains possible for a long period—up to 13 years in the present series—after the primary infection. —[From the author's summary.]

TUBERCULOUS MENINGITIS

1309. **Tuberculous Meningitis. A Report on Fifty-four Consecutive Cases of Children Treated with Antimicrobial Drugs and Purified Protein Derivative**
G. Nickerson, O. Morgante, P. N. MacDermot, and S. G. Ross. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **76**, 832–851, Nov., 1957. 1 fig., 17 refs.

This report from McGill University, Montreal, presents the results of treatment of 54 consecutive cases of tuberculous meningitis in children admitted to the Alexandra Hospital, Montreal, between August, 1950, and September, 1955. Streptomycin was given initially in a dosage of 1 g. daily for 200 days intramuscularly and intermittently in a dose of 50 mg. intrathecally. After the first year lower doses (0·5 g. and 25 mg. respectively) were used in view of the very high incidence of deafness and vestibular disturbance. The dose of PAS was 10 g. per square metre of body surface; this drug was frequently vomited. Isoniazid was first used during the third year of the period in an initial dosage of 10 mg. per kg. body weight, reduced to 5 mg. per kg. after 2 weeks. An initial dose of 0·0000025 mg. of purified protein derivative (P.P.D.) was given on the 8th day and, if no reaction occurred, the dose was doubled every 2 days

until a reaction was obtained; the same dose was then repeated 4 days later until no reaction was again observed. Treatment was given in three courses, with rest periods of one week between. The initial course lasted 40 days, with daily intrathecal and intramuscular streptomycin, oral PAS (and/or isoniazid later), and P.P.D. every second or fourth day. After a week's rest a second course lasting 80 days was given in which intrathecal streptomycin was given only on alternate days, the other measures being as before. The third course was similar to the second, and the whole period of therapy was 200 days.

The survival rate was 81·5% (44 out of 54 patients), there being no deaths among the 18 patients treated in the last 2 years. These results compare favourably with other published reports. Sequelae consisted in gross deafness, orthopaedic deformity, optic atrophy, vestibular damage, and intellectual disturbance. The electroencephalogram (EEG) was abnormal in the majority (88·8%) at some time during the active phase of the disease, and with few exceptions remained so; there appeared to be a direct correlation between the severity of the disease and the EEG disturbances observed. Psychometric evaluation revealed varying degrees of mental defect in about one-third of the surviving children.

The bacteriological and pathological findings are described. Most of the 10 deaths occurred in patients with severe brain damage or extrameningeal disease. It is emphasized that therapy should be continued even where the outlook appears hopeless. Thus 3 patients who were unconscious for periods of 6 to 14 months made an unexpected recovery followed by remarkably little intellectual impairment. The authors stress the importance of controlling intracranial pressure during the early months of therapy and discuss the part played by P.P.D. in altering and eventually clearing the exudate at the base of the brain. *B. Golberg*

1310. **The Results of Treatment of Tuberculous Meningitis since the Introduction of Cortisone.** (Résultats du traitement de la méningite tuberculeuse depuis l'utilisation de la cortisone)
C. Sarrouy, F. Gillot, A. Raffi, L. Sendra, J. Clausse, R. Sabatini, J. P. Raoux, and E. de Peretti. *Pédiatrie* [*Pédiatrie*] **12**, 719–728, 1957. 10 refs.

The authors, working at the Clinique Médicale Infantile, Algiers, have used cortisone or one of its derivatives as a routine adjunct to chemotherapy in the treatment of 16 children with tuberculous meningitis (9 with bacteriological confirmation). Of these, 10 received hormone treatment from the onset and 6 only after other treatment alone was found insufficient. Streptomycin and isoniazid were given systemically in all cases, but only 8 patients received very short courses of intrathecal treatment with streptomycin, in some cases together with hydrocortisone. The course of systemic cortisone treatment lasted 10 to 15 days in most cases. A single course was given in 10 cases, but 6 patients required the course to be repeated up to 5 times.

There were 11 survivors (69%), including one patient who had just completed treatment at the time of the report, compared with 21 survivors (62%) out of a previous series of 34 patients who were treated without hormones. Of the 16 patients in the present series, 12 were unconscious, with or without paralytic manifestations, on admission, and all the 5 deaths occurred in this group. One of the deaths was probably attributable to haemorrhagic chicken-pox which developed during hormone treatment [a recognized hazard]. In the other 4 fatal cases no improvement was noted at any time, and death took place between the 9th and 28th days after admission. In the survivors clinical improvement was rapid, consciousness returning within a week or so in most cases and the speed of recovery in other respects being spectacular compared with the authors' previous experience. However, it was usually some 3 months before the cerebrospinal fluid became normal. Three patients relapsed on discontinuing treatment, and 2 survivors had residual paralyses. There were no cases of spinal block.

[The results in this series are no better than could be obtained in Great Britain even before the introduction of isoniazid, but the type of case is obviously different and the conditions in the two countries are probably not comparable. Nevertheless, the authors' enthusiasm for their method of treatment is not substantiated by an impassive analysis of their cases, and there are many fallacious statements in their paper which are often due to too much reliance being placed on results from a very small number of cases.] *John Lorber*

LYMPHADENITIS

1311. **Tuberculous Cervical Adenitis**
T. J. Wilmot, E. F. James, and L. V. Reilly. *Lancet* [*Lancet*] **2**, 1184–1187, Dec. 14, 1957. 1 fig., 15 refs.

The authors describe an investigation of 81 cases of tuberculous cervical adenitis seen in Counties Tyrone and Fermanagh, Northern Ireland, between November, 1951, and July, 1956, which was undertaken in an attempt to resolve the existing conflict of opinion as to the aetiology and pathogenesis of this condition and to decide on a definitive line of treatment. Most of the patients were aged between 5 and 9 years, but the age range was from 3 to over 55 years. The commonest sign was an enlarging lump in the neck; pain or constitutional upset was rare. In 71 cases a single group of lymph nodes was diseased, this being the deep cervical group in 60 cases, the submandibular in 5, that in the posterior triangle in 3, the supraclavicular in 2, and the facial in one; in the remaining 10 cases two or more groups of nodes were affected. Active pulmonary tuberculosis was present in 4 cases, healed pulmonary tuberculosis in one, and 17 patients had a previous history of tuberculosis, of whom 12 had had an earlier attack of cervical adenitis, the history in 2 of these cases extending over more than 20 years.

Specimens of aspirated pus or tissue from excised nodes, tonsils, or adenoids were obtained from 54 patients and examined bacteriologically, tubercle bacilli being seen in 41 (76%). However, culture of the organisms was

successful in only 4 cases, the human type of tubercle bacillus being grown in 3 and the bovine type in one. Tonsillectomy was performed in 47 cases, the tonsils being examined histologically in 30 and tuberculous infection observed in 14. Examination of radiographs of the chest of 75 patients revealed signs of a healed primary focus in 38 (51%). From these findings the authors conclude that tuberculous cervical adenitis usually develops from a primary infection of the tonsil which is caused by aspiration and is synchronous with a primary infection of the lung. The infection in the cervical nodes may be dormant for months or even years, but an attack of tonsillitis is likely to bring it to light. Tubercle bacilli are difficult to grow from cervical nodes, but the authors' experience of primary tuberculous infections elsewhere in the body leads them to believe that such infection is usually caused by the human bacillus.

Their management of a case has been as follows. After a full clinical examination, radiography of the chest, and tuberculin testing (44 out of 50 proved cases were tuberculin-positive), prolonged chemotherapy with PAS and isoniazid is given when the disease is bilateral and when extension to the mediastinal lymph nodes is suspected; surgery in these cases is confined to aspiration and curettage, with perhaps local excision later, but calcified nodes should not be excised. Surgery under chemotherapeutic cover is used in the other cases. If there is no softening or fluctuation of the nodes or other indications of abscess formation, tonsillectomy, adenoidectomy, and dental hygiene are performed first, and this may result in subsidence of the swelling. If it persists chemotherapy is given, but if it increases excision is indicated. Aspiration with curettage alone was performed in 11 cases, in 6 of which, however, excision of a node was required later. Excision of nodes was performed on 54 patients, in 3 of whom there was a recurrence followed by another excision. The results have been generally good, and no skin grafting was required. The authors have found a long rest unnecessary for these patients, most of whom return to school within 3 weeks of leaving hospital. *Arthur Willcox*

1312. **Tuberculous Hilar and Mediastinal Adenitis. Course, Prognosis, and Ambulatory Chemotherapy**
D. N. SHIVPURI and B. BAN. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **76**, 799–810, Nov., 1957. 1 fig., 15 refs.

At Old Delhi, India, 287 cases of hilar and mediastinal adenitis due to tuberculosis were studied over a 30-month period. The incidence in females was 2·3 times that of the males, and the maximal incidence occurred at a later age (10 to 20 years) among females than among males (3 to 10 years).

A positive tuberculin reaction was obtained in 100% of the patients tested. Tubercle bacilli were demonstrated in 23% and a history of contact with active tuberculosis was obtained in 33% of the patients. Associated tuberculous lesions were present in about 75% of females and 60% of males. Such complications as pleural effusion or parenchymal lesion were more common in females, while cervical and axillary adenitis predominated in the males. Atelectasis (segmental or lobar) was detected in 9% of the patients and was most common in the right upper lobe.

Of the 287 patients 136 (47%) were followed for a period of 3 months to 5 years (average period, 14 months). One-third of these received no chemotherapy; the remainder received chemotherapy for varying periods ranging from 4 to 32 weeks. Marked or moderate enlargement of the mediastinal lymph nodes was present in about 80% of both treated and untreated groups, but significant improvement was noted in only 8·6% of the untreated group, as opposed to 41·2% of the ambulatory chemotherapy group. Ambulatory chemotherapy proved to be practical in this situation. The value of prolonged antituberculous chemotherapy was stressed by the finding that improvement became more marked, while unsatisfactory results became less frequent, the longer chemotherapy was continued. Chemotherapy for at least one year would seem to be indicated for all cases of tuberculous hilar and mediastinal adenitis.—[From the authors' summary.]

1313. **The Current Status and Treatment of Lymphatic Tuberculosis. A Review Based on the Experience with 120 Cases**
J. M. SCHLESS and J. A. WIER. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **76**, 811–831, Nov., 1957. 32 refs.

Among 3,958 adult patients with active tuberculosis seen at Fitzsimons Army Hospital, Denver, Colorado, in the 4-year period 1952–5, 120 cases of significant lymph-node tuberculosis were found. The incidence was higher among negroes (45·8%) than in white patients (26·7%). The cervical and mediastinal lymph nodes were those most commonly affected. Almost half of the patients (58) had additional significant tuberculous disease either before, during, or after admission to hospital, this being pulmonary in location in 50, while 29 of the cases represented a recurrence of the tuberculous adenitis in patients who had been treated before the chemotherapeutic era, or with inadequate (one drug only) or insufficient chemotherapy. Only one patient in the present series relapsed, having discharged himself after only 3 months' treatment. At present these patients are treated with either isoniazid and PAS or isoniazid and streptomycin usually for 18 to 24 months, at least 300 mg. of isoniazid being given daily. In cases so treated there is a fairly rapid recession of the more acutely inflamed lymph nodes and also of any generalized systemic manifestations. Surgery is indicated only for removal of fluctuant nodes in imminent danger of rupture, and for the removal of symptomatic atelectatic or bronchiectatic lung areas after adequate chemotherapy.

Of 50 of the 120 patients who were followed up for more than 2 years, 48 were apparently well and were working; the other 2 were lost to follow-up near the end of the study. Among the remaining 70 patients, apart from 36 transferred elsewhere while still under active treatment, there are no known cases of currently active or reactivated disease. *B. Golberg*

Venereal Diseases

1314. **The Epidemiology of Syphilis and Possible Factors in the Present Tendency towards Its Recrudescence.** (Épidémiologie de la syphilis et facteurs éventuels de la tendance actuelle à sa recrudescence)
A. TOURAINE. *Presse médicale* [*Press méd.*] **65**, 1851–1854, Nov. 16, 1957. Bibliography.

It is widely believed that the incidence of syphilis has fallen dramatically in the last 20 years and that the disease may soon disappear entirely. But the author of this article, in discussing the epidemiology of syphilis, suggests that the statistics may be misleading and that there are dangerous factors which have caused a recrudescence of syphilis in the past 3 years and which could result in a considerable increase in morbidity. In France the incidence of primary and secondary syphilis fell between 1946 and 1955 by 92%, in Italy between 1937 and 1951 by 87·6%, and in the U.S.A. between 1947 and 1952 by 88·9%. In regard to these figures the author emphasizes that present-day incidence should be compared with pre-war figures of incidence rather than with those of the immediate post-war epidemic era, and that by such a comparison the present reduced incidence of syphilis is shown to be much less striking. There has always been a tendency to fluctuation in the incidence of venereal diseases throughout the world, with a gradual trend towards a lower level. A periodicity of 8 to 15 years between the upward trends is noted. These movements in incidence were observed long before the discovery of new therapeutic measures, such as antibiotics, and may occur apart from wars or movements of population. Such an era of higher incidence of syphilis appeared to start during the period 1955–7.

Serological tests for syphilis have not shown a fall in positive results comparable to the reported fall in incidence of cases of early syphilis. In France positive serological reactions for syphilis are found in about 1% of the population, and many of these are believed to be due to recent infection, so that the official returns of the incidence of recent syphilis may be much lower than the reality. Similar statistics are quoted for the U.S.A. and for most of the countries of Europe, in all of which treatment and preventive measures against venereal disease are well organized.

The factors which favour recrudescence of syphilis are partly international and partly national. Among these are the ignorance of the public in regard to sexual matters and the dangers of venereal disease, ignorance or lack of vigilance among the medical profession, and indifference of public health authorities to the tracing of contacts and other epidemiological measures. General factors, such as economic conditions, are also important: for example, it has been noted that syphilis tends to increase during periods of national prosperity, when increased spending power results in flourishing prostitution. Movements of the population, as well as public holidays and celebrations, are further contributory factors; for example, Rabut reported an increase in the number of clients of brothels after the celebrations for Lindbergh's transatlantic flight and also after funerals of nationally important public personages. In the author's opinion the spread of syphilis is predominantly due to certain social categories of persons, such as prisoners, immigrants, prostitutes, and foreign workers who, as a group, are more heavily infected than other categories. In certain parts of the world there are reservoirs of syphilis which are a danger to all other countries. The efforts of the World Health Organization in collective treatment are likely to be very helpful in this respect, but special measures to prevent the importation of syphilis from these areas of high incidence may have to be adopted by the healthier countries.

Robert Lees

1315. **Study of the Antigenic Structure of *Treponema pallidum* by Specific Agglutination**
P. H. HARDY and E. E. NELL. *American Journal of Hygiene* [*Amer. J. Hyg.*] **66**, 160–172, Sept., 1957. 2 figs., 16 refs.

Various tests have recently been introduced for the demonstration of specific antibodies to pathogenic treponemes in which whole treponemes are employed as the antigenic component. Discrepancies between the results of the several tests have suggested that different antigen–antibody reactions are involved in them, implying that *Treponema pallidum* has a complex antigenic structure.

The authors have therefore attempted to clarify this structure in experiments carried out at the Johns Hopkins University, Baltimore. Suspensions of killed treponemes from syphilomata of the testes of rabbits infected with the Nichols strain were used to obtain immune sera from adult animals. All Wassermann antibody was removed from these sera by absorption with beef heart preparations, ethylenediamine tetra-acetate (EDTA) was added to bind divalent cations, and agglutination tests were then performed with suspensions of *T. pallidum*.

Heating, reduction of *p*H, and the presence of divalent cations were found to affect the results. It was also found that freshly prepared treponeme suspensions were less readily agglutinated than suspensions which had been stored at 4° C. [This would suggest either the existence of a physical barrier (such as a capsule or slime layer) preventing the combination of antigen with antibody until it has been removed by enzyme or other action or the presence of such a large quantity of surface antigen that all available antibody is absorbed by relatively few organisms.] Since a direct relation was demonstrated between agglutinability and antibody-combining capacity, however, the latter explanation can be excluded. The former explanation is supported by the finding of Turner and Hollander that the addition of hyaluronidase (or

of factors hindering its inhibitors) increased the agglutinability of treponeme suspensions, indicating the existence of a mucopolysaccharide coat. Evidence is presented which suggests that syphilitic immune serum contains two specific antibodies, the antigenic component of the treponeme which reacts with one of these being inactivated by both heat and trypsin, whereas the other appears to be stable to these agents. The authors point out that while Portnoy's complement-fixation reaction, which is the only treponemal serological test that does not employ whole organisms, should for that reason approach most closely to a single antigen–antibody system, it is quite possible that, here too, multiple reactions are involved. *Allene Scott*

1316. **Streptomycin for Gonorrhoea in London in 1956.** [In English]
R. R. WILLCOX. *Acta dermato-venereologica* [*Acta derm.-venereol.* (*Stockh.*)] **37**, 332–337, 1957. 5 refs.

The investigation described in this paper from St. Mary's Hospital, London, was designed to determine whether gonococci isolated from patients under treatment in the London area showed any evidence of increasing resistance to streptomycin. In 1951 the author reported the results obtained with streptomycin in the treatment of 62 patients suffering from acute gonorrhoea (*Brit. J. vener. Dis.*, **27**, 92; *Abstr. Wld Med.*, **10**, 413). In 33 out of the 52 who remained under observation for varying periods treatment was thought to be successful; of the remainder, 8 were treated for residual non-gonococcal urethritis, 5 failed to respond, and 6 were alleged to have been reinfected. In 1956 a further 109 patients suffering from acute gonorrhoea were treated with streptomycin, a single injection of 0·5 to 1 g. being given. Of 88 patients who remained under observation, 53 responded to treatment; 18 were treated for residual non-gonococcal infection, 11 for gonorrhoea which failed to respond, and 6 were alleged to have been reinfected. The failure rate was not significantly greater in 1956 than in 1951. In the second series the results with a dosage of 1 g. were much the same in white patients as in negroes, but with a dosage of 0·5 g. the failure rate in negroes was significantly higher than that in white patients, for reasons which, the author states, were obscure. *A. J. King*

1317. **Long-acting Penicillin in Gonorrhoea Control**
M. J. TAKOS, L. W. ELGIN, and T. E. CATO. *Public Health Reports* [*Publ. Hlth Rep.* (*Wash.*)] **72**, 976–980, Nov., 1957. 4 refs.

In this report of a joint anti-gonorrhoea campaign carried out by the Dade County Health Department, Florida, and the University of Miami School of Medicine the authors point out that the problems in controlling gonorrhoea are chiefly related to the frequent absence of symptoms of the disease in infected females and to the difficulty of demonstrating the infection bacteriologically in such cases. In an attempt to decrease the rate of spread of gonorrhoea in Dade County, all female contacts of male patients with gonorrhoea were treated with 2·4 mega units of benzathine penicillin (1·2 mega units injected into each buttock). As such a dose has been reported to maintain a therapeutic level of the antibiotic for at least 6 weeks it was thus hoped to cure the gonorrhoea present in these women and to protect them from reinfection for approximately 6 weeks. Meanwhile the male patients were treated with 600,000 units of 72-hour repository (procaine) penicillin and could therefore be reinfected sooner, so providing the most effective way of locating infected females.

This programme of treatment was begun in June, 1954, and there was an apparent immediate decrease in the number of proven cases of gonorrhoea, the average of 180·1 cases per month for the first 6 months of that year falling to 146·8 cases per month for the last 6 months. This decrease has continued, and from a table given it is seen that the mean monthly average of cases was 136·1 for the year 1955 and 122·0 for 1956. During the years under survey the morbidity rate per 1,000 of the population in the area fell from 3·1 in 1954 to 2·4 in 1955 and to 2·1 in 1956. Over the same period the incidence of gonorrhoea in two neighbouring metropolitan areas in Florida showed a rise in one and no significant change in the other. The massive doses of penicillin used did not produce more allergic reactions in patients than did smaller doses, and pain in the buttocks, when it occurred, usually did not last for more than 24 hours. The authors conclude that the use of long-acting penicillin will not immediately eliminate gonorrhoea from a population; however, it should offer the possibility of a steady, slow decline [unless, of course, the method contributes towards the production of a penicillin-resistant strain of gonococcus]. *Benjamin Schwartz*

1318. **Treatment of Non-gonococcal Urethritis with 2-Acetylamino-5-nitrothiazole ("Aminitrozole") Given Orally.** [In English]
R. R. WILLCOX. *Acta dermato-venereologica* [*Acta derm.-venereol.* (*Stockh.*)] **37**, 327–331, 1957. 4 refs.

It has been claimed that "aminitrozole" (2-acetyl-amino-5-nitrothiazole), given by mouth, is an effective remedy for trichomonal infection of the genito-urinary tract, although this claim has not been substantiated in Britain. The present author, at St. Mary's Hospital, London, used this preparation in the treatment of 49 male patients suffering from non-gonococcal urethritis. Of 28 cases in which the urethral secretion was examined for the presence of *Trichomonas vaginalis* by dark-field microscopy of wet specimens, the organism was found in only one. The dosage of aminitrozole was 100 mg. 3 times a day for 6 to 10 days. There were no toxic effects. Altogether 45 patients were followed up, although only 15 remained under observation for more than one month. There were 22 known treatment failures, these results being much the same as those obtained in 29 cases in which a placebo was given. It is concluded that aminitrozole is not a useful drug in the treatment of non-gonococcal urethritis. The fact that gonococci were found in the secretions of 6 of these patients on later microscopical examination suggested that there had been further sexual contact during the period of observation. *A. J. King*

Allergy

1319. **Allergy to Estrogens. Critical Evaluation of Tests with Oil Preparations**
J. REBHUN. *Annals of Allergy* [*Ann. Allergy*] **15**, 647–657, Nov.–Dec., 1957. 3 figs., 17 refs.

The case is described of a female patient who reacted to the oral administration of oestrone and diethylstilboestrol with sneezing, rhinorrhoea, swelling of the cervical lymph nodes, and fever, symptoms which readily disappeared after taking antihistamine drugs. Skin tests with a watery solution of oestrone and with oily solutions gave positive reactions of the delayed type. In tests on 8 control subjects none reacted to aqueous solutions, whereas 5 gave delayed positive reactions to oily solutions of oestrogens and to the cottonseed-oil vehicle. It is concluded that positive skin reactions to oily preparations of oestrogens are mainly due to the action of the vehicle.

H. Herxheimer

1320. **Personality Variations in Bronchial Asthma**
P. H. KNAPP and S. J. NEMETZ. *Psychosomatic Medicine* [*Psychosom. Med.*] **19**, 443–465, Nov.–Dec., 1957. 1 fig., 36 refs.

A clinical investigation of 40 subjects with active perennial bronchial asthma is reported from the Boston University School of Medicine, the aim of which was to determine: (1) whether the subjects showed any psychological disturbance and, if so, of what sort; (2) whether they showed psychotic reactions; and (3) whether there was any other relationship between variations in personality and variations in the degree or type of asthma. The age range of the patients was 17 to 59 (median 29·5) years, and 70% were males, in contrast to the approximately equal sex distribution reported by most authors. A family history of allergic disease was noted in 23 of the 40 cases. For the purpose of the investigation 2 psychiatrists collaborated with 2 physicians. The former conducted between 5 and 400 (median 45) psycho-analytically orientated interviews with each patient, while the latter carried out measurements of timed vital capacity and other tests of pulmonary function.

A wide range of pulmonary disorders, as well as disturbances of personality, were discovered among the patients. It was noteworthy that no subject was judged to be free from overt psychological disorder. Generalizations about all asthmatics in this respect are, however, unwarranted, since the sample may not have been a representative one. Seven short-lived psychotic episodes, accompanied by an increase of asthma, were observed and these did not appear to be closely associated with steroid therapy. No valid support was found for the theory that a reciprocal relationship exists between asthma and psychosis.

The emotional maturity of the patient was gauged on a quantitative scale employing clinical criteria and was compared with a quantitative evaluation of the degree of pulmonary disease. It was found that the more severe the pulmonary disturbance, the more severe was the personality disturbance, the latter often antedating the onset of the asthma. The general conclusion is reached that bronchial asthma is merely one of many ways in which unresolved emotional problems may become clinically manifest. The analysis of the findings is supplemented by 4 illustrative case histories.

A. Balfour Sclare

1321. **Sources of Tension in Bronchial Asthma**
P. H. KNAPP and S. J. NEMETZ. *Psychosomatic Medicine* [*Psychosom. Med.*] **19**, 466–485, Nov.–Dec., 1957. 1 fig., 22 refs.

A further study of a group of 40 chronic, non-seasonal asthmatic subjects is reported from the Boston University School of Medicine [see Abstract 1320], the aim of which was to investigate the major areas of emotional conflict in bronchial asthma. The study extended over 3 years, and the authors' contact with the patients varied from anamnestic appraisal to intensive psycho-analytical therapy.

In respect of position in the family and age of younger siblings the patients did not differ significantly from a comparable group of psychoneurotic patients, but a higher proportion of those over 21 were, or had been, married. Certain broad areas of conflict were found to be frequent sources of tension. These included passive-dependent attitudes (as illustrated by inadequate social, marital, and occupational adjustment), chronic feelings of shame and depression, and unsatisfied oral needs (exemplified by preoccupation with food, weight, and alimentary symptoms). A number of more localized areas of conflict were also delineated as sources of tension. Among these were nasal and olfactory preoccupations (such as hyper-reactivity to odours), neurotic attitudes to water (such as intense longing for the sea or dread of water), conflict over crying, concealment, and confession, and preoccupation with the voice, not only for its content but more specifically for its motor and acoustic qualities. This last attitude was present in 30 (75%) of the subjects.

A final source of emotional tension in 22 of the 40 patients appeared to be their "exposure" to respiratory illness in persons important to themselves before the onset of their asthma. More often than not such respiratory illness was of a type generally acknowledged to be non-allergic. Early "exposure" of this type to respiratory illness is considered by the authors to be partly responsible for a process of psychosomatic conditioning in asthma. It is suggested that the oral-nasal-vocal-respiratory apparatus may be sensitized in different ways in different asthmatic subjects, and that one such way may be through identification with the respiratory pattern of other individuals.

A. Balfour Sclare

Nutrition and Metabolism

1322. A Syndrome of Osteoporosis in Africans and its Relationship to Scurvy

H. GRUSIN and E. SAMUEL. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] 5, 644–650, Nov.–Dec., 1957. 1 fig., 28 refs.

The authors have investigated the association of osteoporosis and scurvy among the South African Bantu, only patients being selected for study in whom radiography of the spine showed crush fractures or biconcave vertebral bodies in association with osteoporosis for which no obvious cause could be found; those with radiological evidence of only diminished bone density were excluded. During a period of one year 16 patients (12 male and 4 female) at the Baragwanath Hospital, Johannesburg, fulfilled these criteria; all but 2 of these were under 60 years of age. The results of clinical, radiological, and laboratory studies are presented, together with the post-mortem findings in 2 patients who died. Liver biopsy revealed gross haemosiderosis in all of 7 patients examined and portal fibrosis in 6 of them; tests of liver function showed that this was grossly abnormal, the albumin : globulin ratio of the serum proteins was reversed, but the serum calcium and plasma phosphorous levels were within normal limits, except in 2 cases in which the serum calcium level was below normal.

Of the 16 patients, 9 were also suffering from acute scurvy, one had a haemorrhagic pericardial effusion which was considered to be a " scorbutic equivalent ", and one had a past history of scurvy; thus 11 patients (69%) were or had been scorbutic; the remaining 5 patients presented no evidence of past or present scurvy. The administration of 500 mg. of ascorbic acid daily by intramuscular injection resulted in the complete disappearance of the signs of scurvy within 4 to 6 weeks. This treatment, together with 15 g. of calcium gluconate daily by mouth, was continued in 6 patients for a long-term trial; after observation for 9 months to 3 years all except one showed progressive increase of osteoporosis, as judged by further vertebral collapse.

It is generally accepted that a low dietary intake of calcium, abnormal blood protein levels, haemosiderosis, and scurvy are among the factors which, singly or together, may be responsible for osteoporosis. The authors point out, however, that these conditions, with the exception of scurvy, are common to the majority of African patients. In fact both scurvy and osteoporosis are uncommon diseases at this hospital, yet these relatively rare conditions were frequently found in the same patient. Moreover, the incidence of osteoporosis among a group of 48 patients with typical acute scurvy was 18·7%, whereas no case of osteoporosis was found in a group, selected at random, of 150 non-scorbutic subjects of the same age and sex. In the authors' view the evidence suggests that chronic deficiency of ascorbic acid, often unrecognized, may be responsible for osteoporosis in the Bantu. *Joseph Parness*

METABOLISM

1323. Changes in Iron Metabolism following Gastrectomy and Other Surgical Operations

I. MCL. BAIRD, D. A. PODMORE, and G. M. WILSON. *Clinical Science* [*Clin. Sci.*] 16, 463–473, 1957. 2 figs., 25 refs.

During an investigation of the pathogenesis of the anaemia which sometimes occurs after gastrectomy a marked fall in the serum iron level was observed after the operation; a similar fall was seen in patients subjected to other surgical procedures. In an attempt to determine the mechanism of this hypoferraemia the authors, at the Royal Infirmary, Sheffield, studied the serum iron concentration and the serum unsaturated iron-binding capacity before and after operation and at intervals after a dose of ferrous sulphate in 20 patients undergoing gastrectomy and 43 subjected to less severe operations. In some cases radioactive iron (^{59}Fe) was given with the ferrous sulphate and absorption of the isotope studied, faeces being collected and homogenized in water to estimate the total amount of ^{59}Fe which had been absorbed.

The serum iron level fell from a mean of 133 μg. per 100 ml. before gastrectomy to a mean of 75 μg. per 100 ml. 2 weeks afterwards; it rose to 129 μg. per 100 ml. 3 months after operation, although there was no associated change in the haemoglobin concentration. The pattern of response in the serum iron level following oral administration of ferrous sulphate " was essentially similar " before and 3 months after gastrectomy, but 2 weeks after operation the rise was very small. There was no change on these three occasions in the excretion of ^{59}Fe.

In 37 patients undergoing other surgical procedures there was a definite fall in the serum iron level 48 hours after operation. No significant change was observed in the serum unsaturated iron-binding capacity before and 48 hours after operation in 16 patients in whom this value was determined. There was depression of the serum iron level following oral administration of ferrous sulphate in 10 patients. The haemoglobin concentration and packed cell volume, which were determined in 5 patients, showed no significant change.

These findings suggest that the fall in the serum iron concentration is not due to malabsorption, external blood loss, or haemodilution, but represents a change in iron distribution within the body. The authors briefly discuss the possible mechanism of this fall, and note that low serum iron concentrations are also found in acute and chronic infections and in rheumatoid arthritis. It is suggested that the changes are due to metabolic disturbances, although the part played by anaesthetic agents and the significance of the type and extent of the tissue injury in bringing about these changes have not been investigated. *R. F. Jennison*

1324. **Prediction of Serum-cholesterol Responses of Man to Changes in Fats in the Diet**
A. KEYS, J. T. ANDERSON, and F. GRANDE. *Lancet* [*Lancet*] **2**, 959–966, Nov. 16, 1957. 1 fig., 27 refs.

Groups of 12 to 27 men at a time were studied in calorie balance in dietary experiments controlled so that each man was maintained for 4 weeks of standardization and then for 2–9 weeks on each of 2–6 diets differing in fat content, covering the range of 9–44% of calories from fats, with an experimental fat usually representing about three-fourths of the total fat. Fats studied included butter-fat, hydrogenated coconut oil, olive oil, cotton-seed oil, corn oil, sunflower-seed oil, safflower oil, fish oil (*Sardinops cærulea*), and the mixed food fats of ordinary American diets. The intakes of fats, as percentages of total calories provided from glycerides of saturated, monoethenoid, and polyethenoid fatty acids, were estimated for each man on each diet.

These experiments and their analysis offer no support for the suggestion that a deficiency of essential fatty acids produces the high serum-cholesterol levels characteristic of populations subsisting on luxurious American and Western European diets. Effective correction of these high serum-cholesterol levels involves a decrease in the most common fats in such diets and the secondary substitution of fats high in polyethenoid fatty acids.—[From the authors' summary.]

1325. **Alteration of Serum Cholesterol by Dietary Fats**
W. D. ARMSTRONG, J. VAN PILSUM, A. KEYS, F. GRANDE, J. T. ANDERSON, and L. TOBIAN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **96**, 302–306, Nov., 1957. 20 refs.

Serum total cholesterol concentration was measured in 122 young men and 19 young women before and after 9 days during which each person ingested daily 57 g. of corn oil, olive oil, safflower oil or butterfat. The subjects were instructed to follow their usual diets during this period and body weight measurements indicated that the experimental fats did not supplant an equal quantity of ordinary diet calories. The subjects who ingested butterfat showed a slight but statistically insignificant rise in the serum cholesterol while those who ingested the other fats exhibited a statistically significant decrease, averaging 23·0±2·8 mg. per 100 ml. with corn oil, 18·0±4·6 with safflower oil and 10·7±2·3 with olive oil. Compared with the safflower oil the corn oil was more saturated (iodine value 126·7 *v.* 144·2) and contained less linoleic acid (57·5 *v.* 72·0%), so it is concluded that the cholesterol depressant action of the corn oil was not fully accounted for by its degree of unsaturation or content of "essential" fatty acid. Since the subjects in all groups gained some weight, it appears that at least some effects of the 3 vegetable oils tested can be obtained without exact isocalorie substitution in a normal diet.—[Authors' summary.]

1326. **Nutritional Factors and Serum Lipid Levels.** [Review Article]
E. H. AHRENS. *American Journal of Medicine* [*Amer. J. Med.*] **23**, 928–952, Dec., 1957. 8 figs., bibliography.

METABOLIC DISORDERS

1327. **Cardiorespiratory Dysfunction and Polycythemia in Patients with Extreme Obesity**
G. A. LILLINGTON, M. W. ANDERSON, and R. O. BRANDENBURG. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **32**, 585–590, Oct. 16, 1957. 16 refs.

The authors discuss the syndrome of cardiorespiratory dysfunction and polycythaemia with extreme obesity and report 2 cases seen at the Mayo Clinic. The patients, a man aged 44 and a woman aged 28, were apparently free from any primary disease of the heart or lungs, but both were grossly obese and suffered from dyspnoea, cyanosis, somnolence, hypertension, and albuminuria. The man also had pitting oedema of the feet. Clinical and laboratory investigations revealed shallow respiratory movements, polycythaemia, arterial hypoxaemia, and electrocardiographic evidence of an increased load on the right ventricle. In the male patient there was also hypercapnia, which was increased by breathing pure oxygen at the same time as the hypoxaemia was relieved. Reduction in weight as a result of dietary measures was followed by a marked improvement in both cases. The dyspnoea, cyanosis, polycythaemia, and albuminuria disappeared and the electrocardiogram became normal; in the male the oedema and hypertension also disappeared.

The authors suggest that the mechanical interference with respiratory movements resulting from obesity leads to alveolar hypoventilation, and that this in turn causes the hypercapnia responsible for the drowsiness and the hypoxaemia which are followed by cyanosis, polycythaemia, and pulmonary hypertension. They consider that the respiratory centre may show a reduced response to hypercapnia. They find it difficult to explain why these complications are not more commonly found in cases of extreme obesity. *Charles Rolland*

1328. **Evidences for Clinical Magnesium Deficiency**
E. B. FLINK, R. MCCOLLISTER, A. S. PRASAD, J. C. MELBY, and R. P. DOE. *Annals of Internal Medicine* [*Ann. intern. Med.*] **47**, 956–968, Nov., 1957. 2 figs., 39 refs.

Writing from the University of Minnesota, Minneapolis, the authors describe a clinical syndrome characterized by muscle tremor, twitching, and more bizarre movements, occasionally by convulsions, and often by delirium which they state is not uncommon and which can often be shown to be the result of magnesium deficiency. Some animal experiments are described. Study of a large group of patients with chronic alcoholism and tremor, a few postoperative patients, and patients with pyloric obstruction and alkalosis showed that the mean serum magnesium level in 29 patients with delirium and neuromuscular disorders was 1·58 mEq. per litre compared with a mean of 1·88 mEq. per litre in 21 patients with neuromuscular disturbances but without delirium and 2·27 mEq. per litre in a series of healthy subjects and patients without neurological manifestations. The determination of magnesium in the serum and urine was

carried out by a modification of Garner's adaptation of Kolthoff's titan yellow reaction with magnesium.

The case histories of 4 patients (2 alcoholics, one post-operative patient, and one with severe metabolic alkalosis) are presented and the many manifestations ascribed to magnesium deficiency described in further detail. Not all patients showed all the manifestations, but if one of them was severe the others tended to be severe. Study of the case histories indicated that multiple deficiencies, particularly those of vitamins and potassium, were frequently present. Correction of hypopotassaemia might unmask an underlying magnesium deficiency. Partial balance studies on 2 of the chronic alcoholic patients showed that there was retention of magnesium, despite a normal serum level. This finding, together with the time lag of several hours up to one day in response to treatment, suggests to the authors that the essential biochemical defect is a cellular depletion of magnesium. The extracellular concentration of the metabolite gives a poor and therefore sometimes misleading indication of the intracellular concentration.

The administration of magnesium frequently produced a dramatic response. The authors recommend the intramuscular injection of 2 g. of magnesium sulphate (4 ml. of a 50% solution) every 6 hours for 24 hours, followed by 1 g. every 6 hours for 3 to 5 days as a safe schedule which does not cause a hypnotic level of magnesium when renal function is adequate. If magnesium sulphate is given intravenously the dosage should be evenly distributed throughout the various parenteral fluids; the maximum dose should be 5 g. in 1,000 ml. of fluid given in not less than 3 hours. The pathogenesis of magnesium depletion remains obscure. Deficiency may occur during prolonged administration of parenteral fluid, during gastro-intestinal drainage, in chronic alcoholism, and possibly also in primary or secondary aldosteronism.

L. G. Fallows

1329. **A Clinical and Biochemical Study of Hepatolenticular Degeneration (Wilson's Disease)**
H. Bickel, F. C. Neale, and G. Hall. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **26**, 527–558, Oct., 1957. 12 figs., bibliography.

The intensive investigation of 12 patients with hepatolenticular degeneration, here reported from the United Birmingham Hospitals, has served to clarify a number of points raised by the results of recent studies of the abnormal copper and amino-acid metabolism in this disease. These include (1) the familial nature of the malady; there were 4 pairs of siblings among the 12 cases, and other members of the immediate families were found to have similar biochemical abnormalities, though without clinical manifestation of the disease. (2) The early age of onset—in 8 cases the disorder appeared before the age of 11 years. (3) The variability in the clinical picture; although all the patients developed Kayser–Fleischer corneal rings, the neurological signs, such as extrapyramidal disorders, psychoses, mental deterioration, and emotional instability, varied considerably in severity, as did also the signs of hepatic disease, such as recurrent jaundice, abdominal pain, and oedema. Although no major disturbance of renal function was noted, discrete evidence of dysfunction such as proteinuria was obtained.

In the laboratory studies, carried out with due precautions against contamination, frequent estimations of the copper content of the serum and urine revealed in all cases a constant hypocupraemia (30 to 60 μg. per 100 ml.) and cupruria (250 to 1,000 μg. per 24 hours), the extent of which appeared to depend on the severity of the disease. Post-mortem analyses in 2 cases showed a high copper content in the liver, brain, dorsal spinal cord, kidneys, and cornea. Although no abnormality of the plasma amino-acids could be demonstrated, there was usually a marked increase in the urinary excretion of the sulphur-containing and mono-amino-acids and an increase in that of α-amino nitrogen. The level of cupruria was increased even more by the administration of copper-mobilizing or chelating agents such as BAL (dimercaprol), molybdenum, and EDTA (ethylenediamine tetraacetic acid), although therapy with the two first-named agents could not be continued long enough because of toxic reactions. When this report was written no basic alteration in the clinical course of the disease had been achieved with any of the agents, although EDTA given parenterally seemed to be promising.

Discussing the possible pathogenesis the authors suggest that there may be a congenital deficiency in the serum of the laccase, coeruloplasmin, which normally contains 90 to 96% of the total serum copper content, and a consequent increase in the dissociation of the diffusible form of copper from the serum albumin complex, to which it is more loosely bound, thus permitting deposition of the metal in various organs, including the renal tubules. On the basis of this theory treatment should consist in the administration of the copper-removing agent EDTA and of potassium sulphide orally to promote excretion of copper in the stool, together with a diet containing no copper-rich foods, and lastly replacement therapy with pure coeruloplasmin.

Allene Scott

1330. **The Treatment with Antibiotics of Steatorrhoea Eventually Complicated by Massive Hepatic Steatosis.** (Le traitement des stéatorrhées éventuellement compliquées de stéatose massive du foie par les antibiotiques)
J. Caroli, —. Le Quintrec, and —. Reboul. *Archives des maladies de l'appareil digestif et des maladies de la nutrition* [*Arch. Mal. Appar. dig.*] **46**, 613–630, July–Aug., 1957. 20 refs.

The authors report, from the Hôpital Saint-Antoine, Paris, 2 cases of steatorrhoea which responded dramatically to antibiotic therapy, one of them having previously failed to respond to any of the usual measures. The first patient was a man aged 46 who had previously suffered from severe chronic constipation, but more recently had for 2½ years complained of attacks of acute abdominal pain followed by profuse diarrhoea, with fluid stools containing blood. He was severely wasted and had a normochromic anaemia. The stools were extremely bulky and contained large amounts of neutral fat and fatty acid crystals; few meat fibres were present and the carbohydrates were well digested. No amoebae

or cysts were found on repeated examination of the stools and no pathogens were isolated, but cultures were obtained of *Escherichia coli* and *Aerobacter aerogenes*, which were sensitive to chloramphenicol and oxytetracycline. The blood sugar curve was flat and a histamine test meal showed hyposecretion and complete achlorhydria. Radiography after a barium meal revealed volvulus of the stomach accompanied by gross distension and atony of the whole of the small and large intestines, while at laparoscopy oedema and loss of peristalsis of the small intestine, with injection of the epiploic vessels, were observed. Repeated sigmoidoscopic examinations showed no evidence of colitis. The patient did not respond to pancreatic extract, extra vitamins, or a gluten-free diet, nor later to a course of cortisone in doses up to 200 mg. daily; during the treatment with cortisone there was an acute exacerbation of the diarrhoea and an attack of tetany, with a serum calcium level of 6·4 mg. per 100 ml. Blood transfusion improved the anaemia, but had no other effect. The patient responded temporarily to 3 out of 4 courses of chloramphenicol, but on each occasion subsequently relapsed. Cure was eventually obtained with a course of oxytetracycline, which was followed by disappearance of the steatorrhoea and restitution of the body weight and haemoglobin level to normal values.

The second patient was a woman aged 57 years who had a 2-year history of fatty diarrhoea following an operation for strangulated femoral hernia. She was grossly wasted and suffered from peripheral oedema and marked enlargement of the liver. Investigation showed she had a slight anaemia, hypochlorhydria, impaired liver function, and a fatty liver; radiography showed clumping of barium in the small intestine. The stools contained a gross excess of fat; again *Esch. coli* and *A. aerogenes* were cultured, and were sensitive to chloramphenicol and the tetracycline group. The patient responded dramatically to a course of aureomycin, the hepatomegaly regressed, and the liver function improved.

The authors discuss these 2 cases, particularly in the light of studies reported by Frazer and French of Birmingham concerning the role of intestinal bacteria in aggravating steatorrhoea and the isolation of a fat-forming organism from the stools. *Robert de Mowbray*

1331. **The Treatment of Acute Porphyria with Chelating Agents: a Report of 21 Cases**

H. A. PETERS, S. WOODS, P. L. EICHMAN, and H. H. REESE. *Annals of Internal Medicine* [*Ann. intern. Med.*] 47, 889–899, Nov., 1957. 2 figs., 24 refs.

From the University of Wisconsin Medical School, Madison, the authors report on the efficacy of dimercaprol (BAL) and disodium ethylene diamine tetraacetate (EDTA) as chelating agents in the treatment of 21 cases of acute porphyria, 20 of the intermittent type, and one of mixed type. The patients' ages ranged from 22 to 55 years and two-thirds of them were women.

BAL was used in a 10% solution in 20% benzyl benzoate in peanut oil, the dosage ranging from 50 to 1,200 mg. per 24 hours given intramuscularly in divided doses. Treatment usually lasted from 4 to 60 consecutive days, but in several cases one to 3 injections of 100 to 300 mg. were given weekly for as long as 2 years. EDTA was administered intravenously, in a dilution of 2·5 to 5 g. in one litre of 5% glucose in water. The dosage ranged from 1 to 10 g. in a 24-hour period, this being infused over 2 to 4 hours on 2 to 5 consecutive days; a maximum total of 14 days of treatment was reached in one case. Occasionally EDTA was administered orally in the subacute phases of the disease, the dosage being 1 to 3 tablets (of 5 g.) daily. In 11 cases BAL was given alone, while in 6 patients it was combined with intravenous EDTA in the treatment of either acute or chronic phases of the disease, while EDTA was used for preference when there was a history of exposure to lead. Urinary lead excretion levels were borderline in several cases and lead diuresis was noted during chelation. No toxic effects were attributable to either drug or their combined usage.

A good response to chelation treatment was obtained in 4 cases in which ACTH therapy had failed, while conversely in 3 other patients ACTH proved beneficial after a poor response to chelation therapy; 2 patients receiving hydrocortisone for renal failure during chelation therapy responded with a prompt diuresis. All patients had porphobilinogenuria and all but 2 were excreting uroporphyrins; 8 patients showed urinary zinc values ranging from 1·0 to 18·9 mg. per litre (upper normal value 0·5 mg. per litre) before chelation therapy. Zinc excretion values were found to be correlated with the acuteness and severity of the disease, while those of the normal porphyrin metabolites were not; for example, severe clinical symptoms, including convulsions, schizophrenic-like excitement, and tremors, were found in association with urinary zinc excretion 2 to 8 times that of the normal figure in patients with normal urinary porphyrin excretion values and very occasional porphobilinogenuria. The symptomatology common to most of the patients is summarized and 2 case reports are given in detail. The possible modes of action of the chelating agents in the treatment of acute porphyria are discussed, but the exact mechanism of action remains uncertain.

The authors consider that despite the lack of controls, the unpredictability of spontaneous remissions, and the variations in severity characteristic of acute porphyria, their results are favourable, especially in view of the high mortality reported in severe cases by other authors and the prompt response in this series of severely ill patients following chelation. Both the drugs used were found to be effective, although BAL seemed to act more rapidly in some cases. Good nursing and supportive care are necessary for the successful treatment of severe cases. It is stressed that all such patients must avoid exposure to barbiturates, sulphonamides, heavy metals, oil paints, and organic solvents. *L. G. Fallows*

1332. **The Agammaglobulinemias. Relations and Implications.** [Review Article]

C. A. DOMZ and D. R. DICKSON. *American Journal of Medicine* [*Amer. J. Med.*] 23, 917–927, Dec., 1957. 1 fig., 48 refs.

Gastroenterology

OESOPHAGUS

1333. **Observations on the Gastro-oesophageal Junction during Swallowing and Drinking**
B. CREAMER and J. W. PIERCE. *Lancet* [*Lancet*] **2**, 1309–1312, Dec. 28, 1957. 6 figs., 4 refs.

In this paper from St. Thomas's Hospital, London, a study is reported of the behaviour of the gastro-oesophageal junction during the actions of swallowing and drinking, cineradiographs and pressure tracings being obtained simultaneously in 10 healthy medical students. The findings indicated that there is a sphincteric mechanism in the lowest 2 or 3 cm. of the oesophagus and that drinking and swallowing are different physiological processes. In the first of the two series of experiments the subjects held barium in the mouth and swallowed it later when the oesophagus was at rest. The barium was slowly released from the gastro-oesophageal junction after a brief delay and the opening of the junction coincided with a fall in pressure in the area. A sufficiently high intra-oesophageal pressure caused premature opening of the sphincter. In the second series of experiments the subjects drank the same volume of barium from a cup. The barium passed straight through the already widely-opened gastro-oesophageal junction without delay. Moreover, the act of drinking was preceded by a descent of the diaphragm. *A. Wynn Williams*

1334. **Studies in Achalasia of the Cardia**
J. R. TROUNCE, D. C. DEUCHAR, R. KAUNTZE, and G. A. THOMAS. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **26**, 433–444, Oct., 1957. 6 figs., 22 refs.

The authors report, from Guy's Hospital, London, the results of a study in which longitudinal strips of muscle taken from the lower end of the oesophagus during Heller's operation on 7 patients suffering from achalasia of the cardia and also from 5 other patients without achalasia who were undergoing oesophageal resection for other reasons were studied histologically, biochemically, and pharmacologically. Radiological examination of patients with achalasia usually shows a narrowed segment of oesophagus situated below a distended portion, which is hypertrophied and dilated. This narrowed segment, about 2 to 3 cm. in length and just above the cardia, was examined in both groups of patients *in vitro*, the delicate oesophageal muscle being suspended in oxygenated Tyrode solution at 37° C. It was found that this muscle, both from the patients with achalasia and from the others, responded in the same way, contracting to acetylcholine and this response being blocked by atropine and increased by eserine. After the addition of eserine a response was obtained in 4 out of 5 specimens to nicotine which was blocked by hexamethonium, although nicotine alone produced no contraction.

Histologically, active ganglion cells were still present in the muscle from 5 of the 7 patients with achalasia, and biochemical studies showed cholinesterase to be present in the muscle tissue from both groups. The authors conclude that the zone of "tonic" contraction near the cardia, though the lower zone may be otherwise normal, does not relax in achalasia since it is part of an incoordinated mechanism affecting the whole oesophagus concerned in the act of swallowing, and not because ganglion cells are absent in this zone. *Thomas Hunt*

1335. **The Oesophagogastric Sphincter in Hiatus Hernia**
M. ATKINSON, D. A. W. EDWARDS, A. J. HONOUR, and E. N. ROWLANDS. *Lancet* [*Lancet*] **2**, 1138–1142, Dec. 7, 1957. 7 figs., 13 refs.

An investigation was carried out at University College Hospital Medical School and the Central Middlesex Hospital, London, to determine (1) whether the sphincter at the oesophago-gastric junction in normal subjects is due to an intrinsic mechanism or represents external compression by the diaphragm; and (2) whether the occurrence of gastro-oesophageal reflux in cases of hiatus hernia "is correlated with any particular pattern of pressure gradients between the stomach, the hernial sac, and the oesophagus". Intra-oesophageal and intragastric pressures were recorded from fasting subjects lying on their left side by means of open-ended segments of radio-opaque rubber tube (4 cm. long and 2 mm. in internal diameter) connected by air-filled polyethylene tubes to metal-capsule optical manometers, records being made simultaneously from 3 such tubes, the tips of which were spaced at intervals of 4 to 5 cm. The tubes were first passed through the nose until all the recording tips lay below the diaphragm. They were then withdrawn in 1-cm. steps until the distal tube was at least 3 cm. above the oesophago-gastric junction, pressures being recorded at each step for at least 15 seconds.

In tracings from 15 volunteer subjects with no evidence of a hiatus hernia it was easy to distinguish the zones of positive intragastric and negative intra-oesophageal pressure. The position of each recording tip in relation to the diaphragmatic hiatus was identified by the inspiratory swing of pressure in the corresponding tracing, which was positive in the abdomen, negative in the thorax, and commonly biphasic at the level of the diaphragm. Over a distance extending from about 1 cm. below to 2 or 3 cm. above the diaphragm a rise of pressure occurred, which disappeared on swallowing. This band of high pressure was interpreted as representing "a tonically contracted sphincter which relaxes as part of the swallowing reflex", and it is concluded that this segment constitutes a barrier to reflux "because in some parts of it both expiratory and inspiratory pressures were higher

than those in the fundus ". [This conclusion is drawn from observations made on fasting subjects, and the authors make no mention of the fact that after a meal the intragastric pressure may be higher than that in the " sphincteric zone ".] The sphincteric barrier pressure was estimated [? possibly overestimated] by subtracting the mean pressure in the fundus of the stomach from the maximum pressure recorded in the sphincteric zone in 3 or more trial runs. (When a raised pressure was not found in the sphincteric zone it was concluded that the recording tip must have slipped out and another trial was made.) In 7 subjects aged between 20 and 30 the barrier pressure varied from 6 to 15 (mean 9) cm. H_2O. In 8 subjects aged between 40 and 70 the pressure ranged from 1 to 20 (mean 11) cm. H_2O.

In a second series of experiments recordings were made in the same way from 18 patients with a hiatus hernia, 10 of whom were considered to have gastro-oesophageal reflux. The authors' criterion for the diagnosis of reflux is defined as " the presence of pain, discomfort, or a burning sensation which is felt high in the epigastrium or behind the sternum and is brought on or made worse by lying flat, bending, or stooping ". [This definition excludes those patients with reflux but without symptoms of oesophagitis.] These patients' ages varied from 41 to 72. The sphincteric barrier pressure ranged from 7 to 16 cm. H_2O in the 8 diagnosed as having no reflux, but only from 0 to 9 cm. H_2O in the 10 with reflux. From this it is concluded that the sphincteric barrier plays an important part in preventing reflux.

[If a foreign body such as a tube is drawn through the cardia sustained contractions of the lower end of the oesophagus (the vestibule) are commonly seen on the *x*-ray screen. Presumably in the presence of inflammation the lower oesophagus, like any other segment of the gut, will protect itself from injury by not contracting vigorously, so that a high " barrier pressure " would not be expected in patients with oesophagitis. But in any event the pressures recorded from the barrier zone would have to be very much higher than those reported here before the conclusions reached in this paper could be accepted.]

Denys Jennings

1336. **Hiatus Hernia. A Clinical Study of 200 Cases**
V. EDMUNDS. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **26**, 445–466, Oct., 1957. 4 figs., 47 refs.

In this paper are summarized the findings in a series of 204 consecutive patients (161 female and 43 female) suffering from hiatus hernia studied at the Central Middlesex Hospital, London. Following Allison's classification the cases were divided into " sliding " (145 cases), " rolling " (35), and " combined " types of hernia. The conclusions, which confirm previous reports of similar series, showed that in 97% of the cases the hernia was the main cause of the symptoms complained of. In sliding hernia, of which 107 of the 145 cases occurred in women, the main symptoms were pain and heartburn due to gastro-oesophageal regurgitation. In rolling hernia (of which only 3 of the 35 cases were in men) the main feature was anaemia, presumably due to loss of blood. In the causation of hiatus hernia increased intra-abdominal pressure from pregnancy, tumour, or obesity is noted as an important aetiological factor.

[This paper presents a detailed analysis of the condition and, although it brings out no new features, it is based on a large number of cases and for this reason deserves study by those interested in this commonly occurring condition.]

Thomas Hunt

STOMACH AND DUODENUM

1337. **Comparison of Cardiac and Pyloric Sphincters; a Manometric Study**
M. ATKINSON, D. A. W. EDWARDS, A. J. HONOUR, and E. N. ROWLANDS. *Lancet* [*Lancet*] **2**, 918–922, Nov. 9, 1957. 10 figs., 10 refs.

The relationship between structure and function at the oesophago-gastric junction and at the pylorus was studied at University College Hospital, London. By recording the intraluminal pressure from balloons or open ended tubes the authors demonstrated the presence of a sphincter mechanism at the oesophago-gastric junction in 18 healthy subjects and in patients without evidence of hiatus hernia or free gastro-oesophageal reflux. The action of this mechanism was independent of the diaphragm. In contrast, no evidence of a sphincter mechanism at the pylorus was found in 18 healthy subjects, either fasting or with food in the stomach, or in the fasting state in 3 patients with active duodenal ulcer, one with an ulcer in the pyloric canal, and one with hypertrophic pyloric stenosis. From the observations it was also evident that, for the greater part of the time, the pyloric lumen was more than 7 mm. in diameter, whether the stomach was empty or not. [See also Abstract 1333.]

A. Wynn Williams

1338. **A Milk–Alkali Syndrome. Hypercalcemia, Alkalosis and Azotemia following Calcium Carbonate and Milk Therapy of Peptic Ulcer**
J. WENGER, J. B. KIRSNER, and W. L. PALMER. *Gastroenterology* [*Gastroenterology*] **33**, 745–769, Nov., 1957. 40 refs.

The hypercalcaemic syndrome associated with a high intake of milk, alkali, and calcium carbonate is described. During the period 1947–56 3,300 patients with peptic ulcer were placed on a strict dietary regimen of the Sippy type; of this number, 35 developed hypercalcaemia and alkalosis. The authors distinguish between an acute reversible state of hypercalcaemia coming on after only a few days of intensive peptic-ulcer treatment and a chronic state with metastatic calcification and secondary renal damage. The acute syndrome was present in all 35 cases, and there was an " obvious predisposing cause ", such as chronic renal disease, hypertension, or gastro-intestinal haemorrhage, in all except one. The clinical manifestations of the syndrome included nausea, vomiting, anorexia, muscle cramps and weakness, headache, dizziness, and mental changes. Milk and alkali appeared to be equally responsible, while a high dosage of calcium

carbonate (2 to 4 g. per hour) could be given alone to susceptible patients without relapse.

[The 1% incidence of alkalosis in this large series, together with the failure to induce alkalosis in patients with normal renal function by milk and alkali drip, emphasizes the importance of predisposing factors in causing acute alkalosis. The rarer, but more intractable, problem of chronic alkalosis with metastatic calcification is outside the scope of this paper.] *D. A. K. Black*

1339. **Basal Gastric Secretion in Duodenal Ulcer Patients: Its Consideration in Evaluation of Gastric Secretory Inhibitants or Stimulants**

D. C. H. SUN and H. SHAY. *Journal of Applied Physiology* [*J. appl. Physiol.*] **11**, 148–154, Sept., 1957. 12 refs.

From Temple University Medical Center, Philadelphia, an investigation is reported of the variation in fasting gastric secretion in 23 patients with duodenal ulcer, the variation from patient to patient being compared with that in the same patient from day to day. The patients, who were accustomed to the presence of an indwelling stomach tube, fasted for 14 hours before the test. A double tube was used, one part for aspiration of the lower part of the stomach and the other being placed in the duodenum to prevent regurgitation of small bowel contents into the stomach. Saliva was ejected, not swallowed. Specimens were collected every 15 minutes for 6 hours, the first two being discarded. The aspirate of the last hour of the test was also discarded, since psychic secretion increased in anticipation of the meal at the end.

The variation in secretion was considerable. From day to day in the same patient the difference might amount to 500%, and between different individuals the variation rose to three times this figure. It is therefore difficult to assess the effect of a drug on the secretion of gastric juice by comparison with a previous day's secretion or the amount secreted by another patient.

A relationship was found between the secretion in the first hour of the test and the average secretion of the subsequent 4 hours. If the average hourly secretion in the second to the fifth hours was expressed as a percentage of the secretion of the first hour the results from patient to patient were comparable. If a drug was administered and exerted its action during the second to the fifth hours of a test and the average hourly secretion in that time was expressed as a percentage of that in the first hour, this could be compared satisfactorily with results in other patients or with results in the same patient on a different occasion. *A. G. Parks*

1340. **Subtotal Gastric Resection for Peptic Ulcer of Stomach and Duodenum: a Five to Ten Year Follow-up**

L. J. KLEINSASSER, G. G. FALKE, and I. CRAMER. *American Surgeon* [*Amer. Surg.*] **23**, 983–992, Nov., 1957.

A series of 100 consecutive cases of subtotal gastrectomy carried out at the Veterans Administration Hospital, Dallas, Texas, is reviewed, with a 10-year follow-up. The operations were all performed on men for benign peptic ulcer, which was duodenal in 74, pyloric in 10, jejunal in 4, and gastric in 12 cases. The patients' ages ranged from 21 to 80 years. The indications for operation (which were multiple in many cases) were: (1) failure of medical treatment (49 cases); (2) haemorrhage (59, including all 4 cases of jejunal ulcer); (3) previous perforation with subsequent symptoms (22); (4) obstruction (25); and (5) suspected carcinoma (12). The proportion of the stomach resected was between two-thirds and three-quarters, reconstruction being of the Polya type, retrocolic in 96 cases and antecolic in 4. A valve was fashioned in 92 cases, while in cases with a large, adherent duodenal ulcer involving the bile ducts the authors recommend choledochotomy and T-tube drainage.

Immediate mortality was 3%, and postoperative complications, which are detailed, occurred in 12 cases, amongst which were 2 cases of duodenal fistula with survival. Of the survivors, 4 died later of unrelated causes and 71 were followed up for 10 years, the results of operation being considered to be satisfactory in 84·5% and unsatisfactory in 15·5%. The late complications accounting for the latter group included stomal ulcers, which developed at any time up to 6 years after operation, in 8 cases (3 requiring further surgery), dumping (mostly mild) in 13, severe weight loss in one, and anaemia in 2, more than one complication occurring in several cases. In addition, 22 patients in the former group are stated to have suffered from various digestive disturbances of lesser significance.

Andrew M. Desmond

1341. **Gastric Resection: a Definitive Treatment for Perforated Peptic Ulcer**

J. M. EMMETT and H. L. WILLIAMS. *American Surgeon* [*Amer. Surg.*] **23**, 993–1000, Nov., 1957. 27 refs.

The authors report a series of 89 cases of perforated peptic ulcer treated by themselves (66) or their colleagues (23) during the 10-year period 1947–56 by immediate gastrectomy without mortality, comparing the results in this series with those in 287 cases in which elective (non-emergency) gastrectomy was performed. [The latter series is not clearly defined, but it would appear that most of the 287 were treated before 1947, since when the authors have performed immediate resection in the majority of cases of perforation.] A group of 16 cases treated by simple closure during the same period (1947–56) is also discussed.

The authors' hospital is situated in a rural area, and as a result the average interval between perforation and operation was 7·2 (range 2 to 24) hours in 49 of the authors' own cases (17 "walled off cases" being excluded). Of the whole series of 89 cases, 80 were in males and 9 in females; the ulcer was duodenal in 56, gastric in 27, and pyloric in 6; 2 of the gastric ulcers were malignant. The results of immediate gastrectomy were as follows, the corresponding figures for the 287 cases treated by elective gastrectomy being given in parentheses for comparison: mortality, *nil* (2·8%); average stay in hospital 12 days (13·3 days); incidence of recurrence 3·4% (8·4%), of dumping 4·5% (2·8%), and of postoperative complications 24·7% (26·5%). Of the 16 patients treated by simple closure of the perforation, only one died, but half of the survivors developed

recurrent ulcers, more than half of which required further surgery, during the 10-year follow-up period. In spite of the excellent results reported, the authors are hesitant to recommend primary resection for all cases of perforated ulcer; they believe, however, that their experience "establishes a trend which is well worth consideration".

[No distinction has been made in this paper between perforations of acute and chronic ulcers, though the modern tendency is to resect the latter and suture the former. Furthermore, in the absence of any information concerning the distribution of cases in respect of such factors as the age of the patient and the length of the history in the two main series it is impossible to judge whether they are strictly comparable.]

Andrew M. Desmond

1342. **Further Studies on the Pathogenesis of the Postgastrectomy Syndrome**

G. H. PEDDIE, G. L. JORDAN, and M. E. DE BAKEY. *Annals of Surgery* [*Ann. Surg.*] **146**, 892–898, Dec., 1957. 5 figs., 8 refs.

A follow-up study of 33 patients who had earlier been subjected at the Veterans Administration Hospital, Houston, Texas, to subtotal gastrectomy showed that 15 were asymptomatic after eating, but that the remaining 18 suffered from the dumping syndrome. Following the ingestion of a standard hypertonic meal (which is detailed) the following three tests were performed serially. (1) Plasma volume was determined by the use of the dye "T–1824" at 20, 30, 45, 60, 90, and 180 minutes after the meal. (2) Blood samples for estimation of serum potassium level were withdrawn at similar intervals. (3) A continuous electrocardiographic (ECG) recording was taken.

Of the asymptomatic patients, 5 showed plasma volume changes of less than 200 ml., but whereas only 2 out of 16 symptomatic subjects showed changes of the same order, the other 14 with symptoms suffered a fall in plasma volume varying from 97 to 697 ml., with an average of 368 ml., these changes always beginning within 20 minutes of the meal and being maximal within a further 25 minutes. All patients were found to have a lowered serum potassium level after the meal; in the group without symptoms the mean value was 0·88 (range 0·25 to 1·56) mEq. per litre; while in the symptomatic patients the average was 0·97 (range 0·5 to 1·50) mEq. per litre. The onset of this change occurred within 20 minutes of the meal, but the level frequently remained low for 2 hours, that is, long after symptoms had ceased. In 8 symptomatic patients the ECG showed sinus tachycardia, inversion of the T wave, and occasionally other changes. In 5 of 9 patients without dumping symptoms there was no ECG abnormality, but the other 4 showed changes in the ECG similar to the patients with symptoms.

The causes of dumping are discussed. Hyperperistalsis of the small bowel in consequence of undigested food entering the jejunum is considered to be the most important factor. In some individuals this also stimulates the rapid passage of fluid from the blood stream into the jejunum and the resulting loss of fluid from the vascular bed may also be a causative agent, though it is noted that 2 patients with symptoms failed to show any marked change in plasma volume during the test.

A. G. Parks

LIVER

1343. **Effect of Amphenone Therapy on Urinary Excretion of Aldosterone and Sodium in Hepatic Cirrhosis with Ascites**

W. H. J. SUMMERSKILL and J. CRABBÉ. *Lancet* [*Lancet*] **2**, 1091–1095, Nov. 30, 1957. 3 figs., 24 refs.

The synthetic substance "amphenone B" (3:3-di-(*p*-aminophenyl)-butanone-2 dihydrochloride) is a compound structurally related to the synthetic oestrogens which, among its other effects on the endocrine system, depresses adrenal cortical function and causes a decrease in the urinary excretion of aldosterone, with often an associated sodium diuresis. In view of the probable role of the sodium-retaining action of aldosterone in ascites resulting from liver disease the authors, in a trial reported from Harvard Medical School, Boston, have administered amphenone to 4 chronic alcoholic patients with hepatic cirrhosis and ascites in whom the diagnosis was established by clinical and biochemical findings, and in 2 cases confirmed by aspiration liver biopsy. The patients were receiving a diet containing 10 mEq. of sodium; after a period of equilibration observations of body weight, abdominal girth, fluid intake, urinary volume, and urinary sodium excretion were made before, during, and after amphenone therapy. The urinary excretion of aldosterone was measured in 2 cases both as "free" aldosterone (that is, immediately after acidification of the urine) and as "conjugated" aldosterone (that is, the fraction extracted after 48 hours). Prednisone was given as a precaution against toxic effects and was thought not to alter the excretion of aldosterone, but it did lead to a small sodium duresis in one patient.

It was found that 2 patients who had been refractory to conventional therapy showed an increase in urinary sodium excretion from 1 mEq. to 60 to 80 mEq. in 24 hours after amphenone, accompanied by a fall to normal of the previously high urinary aldosterone levels. The other 2 patients derived no benefit from amphenone therapy, but both responded to routine therapy. While no effect of amphenone was demonstrated on liver function or serum electrolyte levels, the 2 patients in whom the sodium duresis was attributed to amphenone developed transient impending hepatic coma. In conclusion the authors consider that the suppression of aldosterone secretion by drugs such as amphenone has a place in the treatment of certain patients with ascites, although more extensive studies are needed and it is hoped that less toxic derivatives will become available.

J. Warwick Buckler

1344. **Bilirubin Metabolism in Jaundice**

B. H. BILLING and G. H. LATHE. *American Journal of Medicine* [*Amer. J. Med.*] **24**, 111–121, Jan., 1958. 4 figs., bibliography.

Cardiovascular System

1345. **Functional Obstruction of the Left Ventricle (Acquired Aortic Subvalvar Stenosis)**
R. Brock. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **106**, 221–238, 1957. 12 figs., 8 refs.

In this article the author pursues the thesis which was put forward in his previous work on functional obstruction to the outflow tract of the right ventricle (*Guy's Hosp. Rep.*, 1955, **104**, 356), and shows that some of the same mechanical effects may also occur in the outflow tract of the left ventricle. The " outflowing part of the left ventricle ", as described by Quain, lies between the aortic cusp of the mitral valve, the papillary muscles, and the interventricular septum. Where it reaches the root of the aorta the walls are more fibrous than elsewhere and therefore not so likely to be obliterated as in its lower part, where longitudinal muscle ridges become prominent on systole.

Congenital aortic subvalvar stenosis, which occurs just below the aortic vestibule, is due to imperfect inclusion of the bulbus cordis in the left ventricle. A ridge of thickened endocardium stretches from the aortic cusp of the mitral valve to the septum and constitutes an obstruction. This form of stenosis is well recognized clinically, and can be treated surgically. A functional type of aortic subvalvar obstruction similar to that seen in the right ventricle is now described by the author as occurring in certain cases of aortic stenosis with gross left ventricular hypertrophy in which, after aortic valvotomy, there is no significant fall in the pressure gradient across the valve despite satisfactory relief of the valvar obstruction. In such cases the only reasonable explanation is the occurrence of a subvalvar stenosis due to the hypertrophic walls of the left ventricle, which had hitherto been held apart as a result of the obstruction to emptying presented by the stenosed valve. Moreover, it is claimed that a similar functional subvalvar stenosis may occur in the complete absence of aortic stenosis as a result of muscular hypertrophy of the left ventricle secondary to systemic hypertension. Details are given of a case in which apparent aortic valvar stenosis developed in the later stages of long-standing hypertension. A presumptive diagnosis of functional subvalvar stenosis was confirmed by cardiac catheterization, which showed the stenosis to lie some 2 cm. below the valve, the absence of valvar stenosis being confirmed at necropsy.

The author points out that left ventricular obstruction of this type may play a significant part in the terminal stages of essential hypertension. It is recognized that in such cases the peripheral blood pressure may fall, this fall being generally assumed to be due to spontaneous remission, to cardiac failure, or to general vasomotor collapse. The real cause, however, may be the occurrence of functional subvalvar obstruction, causing the left ventricular pressure to rise steadily and the strain on the left ventricle to increase even though the arterial blood pressure is reduced. The presence of this state of affairs could be readily demonstrated by simultaneous puncture of the left ventricle and of the aorta and measurement of the pressure gradient between them. He also points out that since in practically every case of aortic stenosis the valve is calcified by the time the patient has reached 40 years, the absence of such calcification in a case of supposed aortic stenosis should suggest the possibility that the obstruction is subvalvar rather than valvar. The importance of making this distinction lies in the fact that if a functional obstruction exists the chances of relieving it surgically are remote at the present time. A stenotic valve can be dealt with, but not a muscle-bound outflow tract. *T. Holmes Sellors*

1346. **A Clinical and Pathogenic Study of the Heart in Severe Anaemia and in Certain Consequent Myocardial Disorders.** (Étude clinique et pathogénique du cœur chez les grands anémiques et dans certains états myocardiaques sequelles)
M. Payet and M. Armengaud. *Presse médicale* [*Presse méd.*] **65**, 1877–1881, Nov. 20, 1957.

In the study of 38 Senegalese women patients with secondary anaemia here reported from the School of Medicine and Pharmacy, Dakar, 28 were found to have an erythrocyte count of less than 1,500,000 and 10 a count of less than 1,000,000 per c.mm. Investigation showed that the primary causes included parasitic infestation, sickling, and haemorrhage, while predisposing states were malnutrition, pregnancy, and " environment ". Of these patients with various types of " tropical anaemia ", 25 were found to be suffering from severe cardiac insufficiency on admission, with " whole-heart " (especially right-sided) failure; the clinical signs are described. Radiology in 31 of the 38 cases showed normal heart size, with pulmonary plethora in 6, while 25 cases showed global, especially right-sided, cardiac enlargement and widening of the pulmonary artery. The electrocardiograms, however, revealed no characteristic change. Determination of the peripheral venous pressure in 20 cases showed that this was normal in only 3 cases with normal heart size and an erythrocyte count of 1·5 million per c.mm.; the remaining 17 patients had venous hypertension ranging from 17 to 29 cm. H_2O. The circulatory rate was accelerated in the 14 cases studied. The plasma protein levels ranged from 4·9 to 8·9 g. per 100 ml., while the albumin: globulin ratio was over 0·7 in 16 cases and below 0·7 in 9 (the normal albumin: globulin ratio in healthy Africans in the locality was 0·9 to 1·0).

The only effective treatment was transfusion of packed erythrocytes, which resulted in clinical improvement in 10 to 30 days, including restoration of normal heart size, as observed radiologically, in 17 of 25 cases. In most cases the pathological state of the " anaemic heart " is absolutely reversible. The authors doubt if the anaemia

alone causes any irreversible cardiac dilatation, but suggest that when this occurs it is due to the combination of anaemia with underlying causes, such as multiple parasitic infestation, and that this may explain the occurrence, for example, of malarial cardiomegaly.

In 12 additional cases sudden severe cardiac failure was evidently precipitated by the incidence of anaemia, which probably revealed previously unsuspected myocardial abnormalities. Details of 3 of these cases which proved fatal are given, and the mechanism of production of the clinical features of the anaemic heart is discussed.

R. S. Stevens

1347. **Prognosis in Subacute Bacterial Endocarditis**
J. WEDGWOOD. *Lancet* [*Lancet*] **2**, 922–925, Nov. 9, 1957. 17 refs.

The prognosis in subacute bacterial endocarditis is discussed with reference to 29 cases seen at Addenbrooke's Hospital, Cambridge, which were followed up after penicillin therapy for an average of 3 years 4 months (range, 1 year 8 months to 9½ years). The patients, 21 males and 8 females, were aged 8 to 81 years. Treatment was with 2 to 10 mega units of aqueous penicillin daily for 6 weeks, 10 of the patients receiving in addition sulphonamides, streptomycin, aureomycin, or chloramphenicol. Of the 29 patients, 11 died, 8 of them from congestive heart failure within 2 years of the start of treatment. The prognosis was poorer in patients with aortic valvular disease (including those with bicuspid valves) with or without mitral stenosis than in patients with mitral valve disease or congenital heart disease. Mortality tended to be highest in middle-aged and older patients and to increase directly with the duration of endocarditis before treatment started. Congestive cardiac failure, cardiac enlargement, and auricular fibrillation at the time of treatment carried a poor prognosis. Haematuria and anaemia were more frequent in the fatal cases than in the series as a whole, but in general symptomatology was not related to prognosis, nor was the rate of fall in temperature with treatment. In 11 patients the cardiac condition was worse following treatment; only 7 patients showed no deterioration.

The author concludes that the long-term prognosis in subacute bacterial endocarditis is still relatively poor in spite of immediate and adequate response to antibiotic therapy.

Gerald Sandler

1348. **Combined Quinidine and Procaine Amide Treatment of Chronic Atrial Fibrillation**
M. J. GOLDMAN. *American Heart Journal* [*Amer. Heart J.*] **54**, 742–745, Nov., 1957. 4 refs.

At the Veterans Administration Hospital, Oakland, California, a group of 38 patients with chronic atrial fibrillation which had failed to revert to sinus rhythm after administration of either quinidine or procainamide alone were given a combination of these drugs in a dosage of 0·2 to 1 g. of quinidine and 0·25 to 0·75 g. of procainamide at 6-hourly intervals. In 19 cases conversion to regular sinus rhythm occurred; thereafter maintained therapy was possible with quinidine alone in 15 cases, both drugs being required in the remaining 4. In 3 cases treatment was discontinued because of nausea and vomiting. Serious ventricular arrhythmia was not observed in any of the cases.

The author suggests that the two drugs combined have a synergistic action rather than a simple additive effect.

Francis Page

DIAGNOSTIC METHODS

1349. **Analysis of Atrial Pressure Curves in the Determination of the Size of an Atrial Septal Defect.** (Analyse von Vorhofdruckkurven zur Grössenbeurteilung von Vorhofseptumdefekten)
F. GROSSE-BROCKHOFF, F. LOOGEN, and H. H. WOLTER. *Zeitschrift für Kreislaufforschung* [*Z. Kreisl.-Forsch.*] **46**, 854–859, Nov., 1957. 5 figs. 1 ref.

It is reported that in the presence of a very large atrial septal defect the left atrial pressure curve fails to rise significantly ("v" wave) during ventricular systole, its level and contour approximating to those of the right atrial pressure curve. This observation was made in the course of the analysis of a large number of pressure curves obtained at the First Medical Clinic of the Düsseldorf Academy of Medicine during the cardiac catheterization of patients in whom the defect was subsequently closed surgically under hypothermia, and was independent of the presence or absence of anomalous pulmonary veins. On the other hand it is stated that when the left and right atrial pressure curves differ significantly during ventricular systole the existence of a large left-to-right shunt into the right atrium indicates the presence of anomalous pulmonary veins without any significant atrial septal defect.

Gerald R. Graham

1350. **Ultrasonic Cardiogram in Mitral Stenosis.** [In English]
I. EDLER and A. GUSTAFSON. *Acta medica Scandinavica* [*Acta med. scand.*] **159**, 85–90, Nov. 15, 1957. 6 figs., 4 refs.

The authors, working at the University of Lund, have developed a technique for the continuous recording of movements of the anterior surface of the heart wall in relation to the surface of the chest. Ultrasonic waves generated in a quartz crystal placed on the surface of the chest and passing into the thorax will be reflected from any interface between two structurally different media. If they strike such an interface perpendicularly they will be reflected back to strike the crystal after an interval which will vary with the distance travelled. If, therefore, after emission of an ultrasonic signal a few millionths of a second in duration the crystal is automatically switched over to receive the signal reflected from the anterior surface of the heart, the time interval between the signal and the arrival of its echo can be displayed visually on the screen of a cathode-ray tube. In practice, signals are emitted and responses recorded alternatively at a frequency of 200 per second. On the screen the position of the starting signal remains constant, forming a straight-line tracing, while the echo signal forms a fluctuating tracing below it, rising and falling with the pulsation of

the heart surface at the point being studied. An electrocardiogram is recorded simultaneously.

By placing the crystal over the third intercostal space 1 to 4 cm. from the left sternal edge a record is obtained which appears to be derived from the movements of the left atrial appendix, and the authors describe the movement pattern at this site in ultrasonic cardiograms obtained from healthy control subjects and from patients with mitral stenosis before and after commissurotomy. They discuss the significance of the differences observed and the information obtainable from such tracings concerning the degree of stenosis present.

[The records reproduced are not of good quality, but this is a preliminary communication only, and the method is an interesting and promising one. The authors' technique and its application have also been described by Effert *et al.* (*Dtsch. med. Wschr.*, 1957, **82**, 1253; *Abstr. Wld Med.*, 1958, **23**, 104).] *J. A. Cosh*

1351. **Catheterization of the Left Heart.** (Cathétérisme des cavités gauches du cœur)

F. Joly, J. Carlotti, M. Servelle, A. Péroz, R. Clin, J. Forman, P. Laurens, N. Azerad, and B. Lucchini. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **50**, 782–800, Sept., 1957. 7 figs., 41 refs.

This comparative study of the transbronchial and transthoracic methods of measuring pressures in the left heart is based on a total of 83 attempts at left atrial puncture carried out at the Hôpital Lariboisière, Paris. The former technique, which was employed on 43 occasions, necessitates bronchoscopy, the atrium being entered from a point near the origin of the left bronchus. In the remaining 40 cases atrial puncture was carried out by inserting a needle into the skin of the back immediately to the right of the spine, at a level determined by the position of a catheter previously placed in the pulmonary artery under fluoroscopic control. In both methods a flexible catheter is introduced through the needle and advanced successively to the left ventricle and the aorta. Since neither technique is without danger the authors advise that left atrial puncture should not be employed as a routine investigation and state that it is definitely contraindicated in ill or feeble patients. (In the present series 4 patients died at intervals varying from 2 days to one month after the procedure.)

The advantages of the transbronchial method are its ease, speed, relatively greater freedom from serious complications, and the fact that preliminary right heart catheterization is unnecessary: on the other hand it is more disturbing to the patient, failure to catheterize the left ventricle is more frequent, and the aorta is only rarely reached. Percutaneous transthoracic puncture does not have these disadvantages, and is more often successful when the left atrium is small; the prone position is, moreover, better tolerated in cardiac disease. Persistent chest pain due to pericardial puncture and pleural effusion are, however, common complications of the direct approach. The authors seem to conclude that each method has its own particular merits. The chief indication for left heart catheterization is disease of the aortic valve. The procedure is of more limited value in the assessment of mitral valvular disease, as left atrial pressure pulses may be recorded with equal accuracy by means of a catheter wedged in the pulmonary artery. *S. G. Owen*

1352. **Catheterization of the Left Heart by Direct Puncture.** (Le cathétérisme des cavités gauches du cœur par ponction directe)

R. Raynaud, J. Houel, M. Brochier, P. Callige, and P. Morand. *Presse médicale* [*Presse méd.*] **65**, 1793–1795, Nov. 6, 1957.

Percutaneous puncture of one or both chambers of the left heart has been carried out on 114 occasions at the Cardiac Surgical Centre, University of Algiers, usually for the purpose of making pressure measurements in patients with mitral valvular disease. In 78 cases left atrial puncture was performed using a fine flexible needle, and in 24 of these was immediately followed by separate puncture of the left ventricle with a similar needle. In addition, left atrial puncture was carried out 34 times with Björk's needle; on each of these occasions an attempt was made to catheterize the left ventricle from the atrium, but this procedure was successful in only 23 instances.

The technique of separate successive puncture of the two chambers is described. With the patient in the prone position the skin of the back is infiltrated with local analgesic at a point selected after the relationship of the right border of the left atrium to the spine has been ascertained by means of fluoroscopy—this is usually about three finger-breadths to the right of the midline at the level of the 7th or 8th intercostal space. The needle, which is 13 cm. in length and has an internal diameter of 0·6 mm., is inclined towards the midline as it is advanced. A characteristic sensation is experienced by the operator as the pericardium and left atrial wall are pierced, when the situation of the needle is verified by aspirating arterialized blood. Intra-atrial pressures are referred during measurement to the level of the thoracic spine and are subsequently corrected for the distance between the spine and the posterior atrial border (estimated from a lateral teleradiograph of the thorax). As soon as the atrial needle has been withdrawn the patient is turned into the supine position and the left ventricle is entered from a point two finger-breadths above and medial to the apex beat; no fluoroscopic control is necessary here. The needle is left in position only for the few seconds necessary for blood sampling and the recording of pressures, which are referred in this case to the anterior axillary line.

Despite the disadvantage that atrial and ventricular pressures can be measured neither simultaneously nor from the same reference level, the authors consider this method to be superior to the Björk technique on the grounds of simplicity and speed, and because it involves less discomfort to the patient and causes fewer complications. Haemoptysis (2 cases) and episodes of paroxysmal tachycardia and 2:1 atrial flutter (one case each) were the only untoward incidents encountered during the 78 punctures performed with the fine needle, whereas the Björk needle, used on 34 occasions, produced a pneumo-

thorax in 3 cases and both haemopericardium and pleural effusion in a fourth. Though the results of these investigations are not presented in detail, some conclusions about the value of measuring left heart pressures in mitral valvular disease are drawn, which are based on 24 cases in which comparison between pressure records and the findings at commissurotomy was possible. The form of the left atrial pulse is an unreliable index of the regurgitation which is associated with stenosis of the mitral valve. On the other hand a prominent " c " wave, frequently intervening between " a " and " v " in tracings from patients with pure mitral stenosis, is a sign of valve suppleness and constitutes a stronger indication for commissurotomy than the absence of a systolic leak. The atrio-ventricular pressure gradient, calculated by superimposing the atrial record upon that subsequently obtained from the ventricle, is a useful supplementary indication of the degree and purity of mitral stenosis, and an appreciable decrease in the gradient after commissurotomy is a sign of a successful operation.

S. G. Owen

CHRONIC VALVULAR DISEASE

1353. **Rheumatic Tricuspid Stenosis**

J. F. Goodwin, S. M. Rab, A. K. Sinha, and M. Zoob. *British Medical Journal* [*Brit. med. J.*] **2**, 1383–1389, Dec. 14, 1957. 14 figs., 27 refs.

The clinical, haemodynamic, and pathological features of organic tricuspid valvular disease are detailed with reference to 21 cases, 13 being observed clinically and 8 studied from necropsy and case records. All the patients (15 females and 6 males) had associated mitral valvular disease, and 12 had aortic disease also. In 15 cases there was a history of previous rheumatic fever. The chief symptoms included dyspnoea (in all cases), paroxysmal dyspnoea, bronchitis, haemoptysis, pulmonary infarction, anginal pain, and hepatic pain. The jugular venous pressure showed a marked or giant " a " wave when sinus rhythm was present or a large systolic wave when atrial fibrillation occurred. Of the total number of cases, 8 were in sinus rhythm. Auscultation revealed a presystolic murmur in the tricuspid area or a mid-diastolic murmur. An early diastolic sound thought to be a tricuspid opening snap was heard in 3 patients. Enlargement of the right atrium was commonly seen in teleradiograms, this enlargement in half the cases being greater than that observed in other forms of valvular heart disease. The electrocardiogram showed pointed P waves, and in 6 of 11 cases prolongation of the P–R interval. Right ventricular hypertrophy was generally absent or slight, never gross. If right atrial enlargement was considerable or gross, right ventricular hypertrophy was usually absent, this being a useful diagnostic feature. Cardiac catheterization was carried out in 8 cases, and the findings, which are tabulated, are stated to be similar to those reported by others.

The authors describe 5 cases in detail to demonstrate the " wide spectrum of organic tricuspid valve disease ". The association of incompetence and stenosis and the differential diagnosis are discussed. *David Friedberg*

1354. **Aortic Commissurotomy: a Physiologic Evaluation by Combined Heart Catheterization**

R. C. Smith, C. P. Bailey, and H. Goldberg. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **34**, 815–828, Dec., 1957. 5 figs., 28 refs.

In order to evaluate objectively the effect of aortic commissurotomy upon aortic stenosis, 14 patients undergoing this operation at Hahnemann Medical College Hospital, Philadelphia, were studied both preoperatively and 2 weeks after operation by combined heart catheterization. After premedication right heart catheterization was performed in the usual way, except that the patient lay prone and a Cournand needle was placed in the brachial artery. For left heart catheterization a 6-inch (15-cm.) No. 18 gauge thin-walled needle was inserted transthoracically into the left atrium under fluoroscopic control. Through this needle a fine polyethylene catheter was then advanced to enter successively the left atrium, left ventricle, and if possible the aorta, so allowing the pressure gradient across the aortic valve to be measured.

The results, which are tabulated, showed that there was a reduction in this gradient in 13 cases, but in only 2 was it abolished completely by the operation. It is suggested that the residual gradient may be due to stiff calcified valves or alternatively to incomplete surgery as a result of the indirect technique employed, the hope being expressed that better results may be expected with the more recent direct-vision techniques. There was a mean increase of 0·3 sq. cm. in the functional area of the aortic valve in 11 cases, and a greater flow through the valve in 9. All 13 patients showed a marked fall in left ventricular pressure. While commissurotomy failed to restore the haemodynamics to normal in most cases, in many it nevertheless relieved the angina, syncope, and dyspnoea. The critical valve area above which these symptoms are relieved is given as 0·6 sq. cm.; in this series the average postoperative valve area was 0·8 sq. cm. The authors state that these findings support the view that early surgical relief of aortic stenosis is desirable in order to avoid advanced secondary valvular deformation and irreversible myocardial damage.

D. Goldman

1355. **The Valsalva Manœuvre in Aortic Valve Disease**

A. E. Doyle and G. H. Neilson. *British Heart Journal* [*Brit. Heart J.*] **19**, 525–531, Oct., 1957. 9 figs., 8 refs.

Assessment of the severity of aortic valvular disease, especially stenosis, has become increasingly important since the introduction of aortic valvotomy. In this paper from the Postgraduate Medical School of London the effects of the Valsalva manœuvre on the arterial pressure pulse in 40 cases of aortic valvular disease are described, with particular reference to the relationship between the variations in systolic upstroke time and pulse pressure. Of the 40 patients, 20 had aortic stenosis, 10 had combined stenosis and incompetence, and 10 had aortic incompetence alone.

The authors found that arterial pulse tracings under resting conditions, the systolic upstroke time, and the pulse pressure were of limited value in assessing aortic

valvular disease, but that the relationship between the changes in pulse pressure and the change in systolic upstroke time during the Valsalva manœuvre were helpful in determining the severity of stenosis and the presence of significant incompetence. This relationship could be expressed as a regression line.

[The method used, which is described in detail, appears to be simple and comparable in accuracy with other methods at present available for the assessment of aortic valvular disease.] *Francis Page*

1356. **Myocardial Fibrosis and Calcareous Emboli in Valvular Heart Disease**
E. D. WIGLE. *British Heart Journal* [*Brit. Heart J.*] **19**, 539–549, Oct., 1957. 6 figs., 18 refs.

To determine whether myocardial ischaemia due to functional coronary insufficiency rather than to coronary arterial disease or rheumatic myocarditis is the cause of myocardial fibrosis in some cases of aortic and mitral stenosis, the author, at the Postgraduate Medical School of London, studied post mortem 7 cases of each type of stenosis by a method in which injection of the coronary artery was combined with careful examination of the myocardium. From the diameter of the three major coronary arteries their total cross-sectional areas were calculated and plotted against the heart weight. For purposes of comparison the necropsy findings in a series of 88 patients with mitral stenosis and 63 with aortic stenosis were reviewed.

It was found that myocardial fibrosis unrelated to coronary arterial disease or rheumatic myocarditis occurred in aortic stenosis, and that the amount of fibrosis was related to the severity of the aortic stenosis and the degree of left ventricular hypertrophy. In mitral stenosis similar fibrosis was seen, but it was less common and less extensive than in aortic stenosis and was almost entirely confined to the posterior wall of the left ventricle. Rheumatic myocarditis was considered to be of little importance in the causation of macroscopic fibrosis. Calcareous emboli were found in coronary arteries in 2 cases of aortic stenosis with calcification of the valve and after valvotomy in one case of mitral stenosis with calcification. *Francis Page*

1357. **Management of the Circulatory, Inflammatory, and Metabolic Complications of Mitral Valvulotomy**
A. V. N. GOODYER and W. W. L. GLENN. *New England Journal of Medicine* [*New Engl. J. Med.*] **257**, 735–743, Oct. 17, 1957. 6 figs., 34 refs.

The operative mortality of mitral valvotomy is generally in the region of 5% in selected cases, but various problems may arise in the later stages in survivors. The authors have examined the various sequelae of valvotomy occurring in a series of about 250 cases treated at the Grace–New Haven Community Hospital, which they classify as circulatory, inflammatory, and metabolic. Their conclusions are as follows.

Circulatory changes are common in the immediate postoperative phase. Hypotension or acute congestive failure with or without auricular fibrillation is comparatively common. Persistent hypotension may require the administration of noradrenaline. No attempt should be made to prevent atrial fibrillation by the prophylactic administration of quinidine, which may cause additional disturbances of conduction, nor should this drug be given immediately if fibrillation arises, but the heart rate should be controlled for 3 weeks or longer before conversion to normal rhythm is attempted. The persistence of cardiac failure after satisfactory valvotomy may be caused by continuing high vascular resistance or another valve lesion; it may also result in atrial fibrillation, which can be controlled by digitalis. Cardiac failure which occurs some time after the valvotomy may be due to a recurrence of stenosis, which is usually caused by an anatomically inadequate operation. Recurrence of rheumatic activity and repeated pulmonary embolism are other possible causes of failure of the cardiovascular reserve. Of the inflammatory sequelae, bacterial endocarditis is the most important, and one that is difficult to control. Pleuropericarditis is a frequent complication occurring early in the postoperative period, and is associated with pain, fever, and effusion. Analysis of the authors' cases suggests that this syndrome is most likely to develop in patients with normal rhythm and very severe stenosis. Pain due to this cause must be distinguished from the pain of the incision and that associated with atelectasis and other complications. No suggestions are made as to its origin. Metabolic disturbances after valvotomy may be disclosed by investigation of the water and salt balance, which frequently shows that the serum sodium and chloride levels are reduced, apparently as a result of excessive water retention (up to 2 or 3 litres a day). Treatment by the infusion of low-salt human albumin preparations, deprivation of water, and possibly by the infusion of hypertonic saline solution should be considered. *T. Holmes Sellors*

1358. **The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life. I. Prognosis with Special Reference to Survivorship**
M. G. WILSON and WAN NGO LIM. *Circulation* [*Circulation*] **16**, 700–712, Nov., 1957. 4 figs., 17 refs.

The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life, with special reference to survival, was studied at the New York Hospital–Cornell Medical Center in the case records of 757 patients out of a total of 1,042 coming under observation since 1916. There were 430 females and 327 males, and at the time of the last follow-up about three-fifths were 30 years of age or over, one-third were over 35, and one-seventh were aged 40 or more. During the period of observation there were 78 deaths in patients who had reached the age of 20—53 from cardiac causes, 8 from bacterial endocarditis (before the introduction of antibiotics), and 17 from other causes or from accidents. The diagnosis was established before the age of 20 years in nearly all the cases, and less than 3% had recurrent carditis after that age. In four-fifths cardiac enlargement was moderate (not detectable clinically) and in one-fifth it was marked.

Mitral insufficiency was diagnosed in 392 patients. Carditis without other major rheumatic manifestation

was observed in one or more attacks in only one-fifth of this group, and was associated with polyarthritis, chorea, or both in about three-fifths. Subcutaneous nodules were observed in 3%. In all except one, cardiac enlargement was moderate. Of 12 deaths in this group, 11 were due to non-cardiac causes and one to bacterial endocarditis. Over the years the murmur regressed in two-thirds of the cases. The over-all average annual mortality was 2·76 per 1,000 compared with 3·1 per 1,000 for the general population. Of the females, 116 experienced 1 to 5 pregnancies.

Physical signs of mitral stenosis and insufficiency, which were present in 269 cases, developed in the majority within 1 or 2 years of an acute attack of carditis. Polyarthritis occurred in one or more attacks in about one-third, chorea in just under one-third, and polyarthritis with chorea in about one-fifth. Subcutaneous nodules were observed in 9%. In only one-fifth of these cases was there marked cardiac enlargement. There were 29 deaths—18 from cardiac causes, 5 from bacterial endocarditis, and 6 from non-cardiac causes; 4 patients died 1 to 5 years after mitral valvotomy. The over-all average annual mortality was 7·8 per 1,000; 93% of the patients survived to the age of 30 years and 86% to 40 years. In this group 112 patients experienced 1 to 5 pregnancies.

In 96 cases there were both aortic and mitral valvular lesions, and in 72 of these cardiac enlargement was marked. One or more attacks of polyarthritis occurred in about one-third, chorea in about one-sixth, and polyarthritis with chorea in rather less than one-half. Subcutaneous nodules were observed in one-third, and in "about one-tenth" the carditis was associated with only minor rheumatic manifestations. Of the 37 deaths, 35 were attributed to cardiac causes. The over-all average annual mortality was 29 per 1,000; 75 of the 96 patients survived to the age of 30, but only 38 to the age of 40. A total of 14 patients in this group experienced 1 to 3 pregnancies.

Increasing cardiac involvement was rarely observed in the absence of recurrent carditis. Cardiac enlargement appeared to be a more important factor in prognosis than the type of valvular lesion. The over-all average annual mortality among patients with moderate enlargement was 3·5 per 1,000 compared with 31 per 1,000 among those with marked enlargement. Of the group with moderate cardiac enlargement at the age of 20, 93% survived to the age of 40, compared with only 40% of those with marked enlargement. There was no evidence that sex influenced prognosis. *C. Bruce Perry*

1359. **The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life. II. Prognosis with Special Reference to Morbidity**

M. G. MAGIDA and F. H. STREITFELD. *Circulation* [*Circulation*] **16**, 713–722, Nov., 1957. 2 figs., 6 refs.

In this second paper on the natural history of rheumatic heart disease in the third, fourth, and fifth decades [see Abstract 1358] the authors report the results of a follow-up examination during the 3-year period 1953–5 of 385 of the original 757 patients, with special reference to prognosis and morbidity. Of the 385 patients (160 males and 225 females), 157 were in the third decade, 176 in the fourth, and 52 in the fifth. There were 173 patients with mitral insufficiency; all were asymptomatic, and in over 70% there was regression of a long-standing apical systolic murmur. None needed surgical treatment. Of 161 patients with mitral stenosis and insufficiency, 27 had symptoms, and of these, 13 might be considered suitable for surgical treatment; in many of the asymptomatic patients there was regression of murmurs. In 51 patients with mitral stenosis and insufficiency there were also aortic valvular lesions; 33 were asymptomatic, and of the remainder some could be considered suitable for surgery.

The records of the 78 patients who died during the 40-year period of the complete investigation were also analysed with reference to morbidity. In 45 of the 53 whose death was attributed to cardiac causes, carditis, auricular fibrillation, pulmonary embolism, and pneumonia were important precipitating factors.

In none of the 385 cases was progressive cardiac enlargement observed with advancing age alone; thus there was no evidence that the valve lesion *per se* was a major factor in the causation of cardiac enlargement. Both morbidity and mortality in the third, fourth, and fifth decades appeared to be more closely related to the cardiac enlargement and the cardiac damage sustained in the first two decades of life than to the type of valvular lesion. Factors responsible for deterioration in the symptomatic status after the age of 20 appeared to be active carditis, auricular fibrillation, bacterial endocarditis, pregnancy, pneumonia, and embolic phenomena.

C. Bruce Perry

MYOCARDIAL INFARCTION AND CORONARY DISEASE

1360. **The Accuracy of Diagnosis of Myocardial Infarction. A Clinico-pathologic Study**

B. C. PATON. *American Journal of Medicine* [*Amer. J. Med.*] **23**, 761–768, Nov., 1957. 31 refs.

The author has assessed the standard of accuracy of present-day clinical diagnosis of myocardial infarction, with and without electrocardiographic assistance, by reviewing the records of 1,646 post-mortem examinations carried out at the Royal Infirmary, Edinburgh, during 1954 and 1955. This showed that out of 266 cases—in 116 of which a recent electrocardiogram (ECG) had been recorded—the clinical diagnosis of recent myocardial infarction (1) was confirmed in 118, (2) was incorrect in 96, and (3) was missed in 52. The final (post-mortem) diagnosis in Group 2 was cardiovascular disease (60 cases), pulmonary disease (16, including 13 cases of pneumonia), postoperative shock or fat embolism (13), and other conditions (7). In Group 3 the clinical misdiagnoses had been congestive or left-sided heart failure (15 cases), pneumonia (4), pulmonary embolism (9), cerebral haemorrhage (6), postoperative shock (5), widespread carcinoma (4), and various other conditions (9); however it was noted that myocardial infarcts were also present in the 6 patients dying from cerebral haemorrhage. Analysis of 132 cases of sudden

death (95 medical cases and 37 surgical), which could not be fully investigated and came to necropsy with only a provisional diagnosis, showed that death was due to myocardial infarction in 74, with previous evidence of coronary arterial disease in 55.

In Groups 1 and 2 the ECG showed evidence of recent myocardial damage (within one month before death), which corresponded to the necropsy finding in 91; there was left bundle-branch block in 3, subendocardial damage in 2, and apical infarction in one. In 15 cases in Group 3 either myocardial infarction had occurred after the last ECG recording or the report had been equivocal. In 37 patients in Groups 1 and 2 not dying suddenly but in whom the ECG was not recorded the diagnosis of myocardial infarction proved correct in only 13 cases. The number of incorrect diagnoses in Groups 2 and 3 (148) was greater than the number correctly diagnosed (118), and about half the sudden deaths were due to recent myocardial infarction.

The author discusses the difficulties encountered in differential diagnosis and the clinical conditions which may mask myocardial infarction, especially in the elderly, and stresses the significance of a previous history of ischaemic heart disease. He concludes: "The electrocardiographic diagnosis of recent myocardial infarction is very accurate, and a clinical diagnosis alone without electrocardiographic corroboration, when this is available, is no longer justifiable." *V. Reade*

1361. **An Anatomical and Clinical Study of Infarction of the Atrial Myocardium.** (Étude anatomo-clinique sur l'infarctus myocardique auriculaire)
A. Gerbaux, R. Piéron, and J. Lenègre. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **50**, 983–996, Nov., 1957. 4 figs., 28 refs.

To 128 examples of atrial infarction collected from the literature the authors have added 8 cases personally examined at necropsy, and on the basis of this material review the pathological and clinical features of the condition. Ventricular infarction is almost always present in addition to the atrial lesion, although the reported rarity of isolated atrial necrosis may, they suggest, be partly due to failure to search for it carefully, except in cases of known cardiac infarction. The overall incidence of atrial involvement in patients with ventricular infarction is probably about 10%. Perhaps owing to the more frequent occlusion of the right coronary artery near its origin, the right atrium is affected much more often than the left (83% and 13% respectively of all reported cases, both atria being involved in the remaining 4%); it has also been suggested that the high oxygen tension of the blood in the left atrial cavity may protect its walls against necrosis. Anatomically, of 92 atrial infarcts, the lesion was localized to the appendage in 59%, to the posterior wall in 14%, and to the lateral wall in 6·5%; the whole atrium was infarcted in 7·5%, and various other sites accounted for the remaining 13%. The associated ventricular infarcts were most often postero-septal or postero-basal and were frequently biventricular. Of 47 reported cases of right atrial infarction resulting from coronary arterial occlusion, only 33 were due to obliteration of the right coronary artery, the other 14 (30%) being apparently determined by a left coronary lesion. This discrepancy is partly explained by anatomical variations in the blood supply of the right atrium, part of which frequently comes from the left coronary artery or its circumflex branch. Left atrial infarction, on the other hand, is almost always associated with occlusion of one of the branches of the left coronary artery, usually the circumflex.

The clinical and electrocardiographic (ECG) features of atrial infarction are discussed. So far as is known, the condition gives rise to no characteristic symptoms. Involvement of the atrial myocardium may be suggested either by the occurrence of atrial arrhythmias (especially fibrillation, flutter, sino-atrial block, and atrial ectopic beats) early in the course of frank cardiac infarction, or by changes in the form of the P wave in the ECG. Although more difficult to detect, the latter are more suggestive of atrial infarction: the changes in the P wave which have been reported are displacement to the right of the P axis (which has been observed in right as well as in left atrial infarction), bifidity, and the development of a Qa wave. Depression of the P–Q segment may occur in healthy subjects and is therefore of doubtful significance. Although inversion of the Ta wave follows experimental atrial infarction in animals, it has never been observed in human patients, even when the presence of A–V block has facilitated identification of the wave. The complications attributable to atrial infarction—namely, cardiac rupture and systemic and pulmonary embolism—are again not characteristic since they occur also, and more often, as a result of ventricular infarction. Embolism is, however, common because of the frequency of intra-atrial thrombosis (in 89 out of 101 reported cases). Atrial rupture occurs occasionally, and accounts for 4 to 7% of all cases of cardiac rupture.

S. G. Owen

1362. **Exercise and Hypoxia Tests in Coronary Insufficiency. I. Electrocardiographic Findings.** (Pruebas de esfuerzo e hipoxia en la insuficiencia coronaria. I. Hallazgos electrocardiográficos)
M. Romero Quiroz, J. E. de la Peña, and E. Cabrera Cosío. *Archives del Instituto de cardiología de México* [*Arch. Inst. Cardiol. Méx.*] **27**, 533–539, Sept.–Oct., 1957. 3 figs.

The authors, working at the National Institute of Cardiology, Mexico, have sought to resolve the many differences of opinion that exist as to the value of certain types of test in the diagnosis and management of cases of coronary insufficiency by studying the effects of exercise and hypoxia on the electrocardiogram (ECG) in 58 subjects. These comprised: (A) 25 healthy subjects; (B) 13 patients with hypertension but with no evidence of coronary disease; and (C) 20 patients with coronary arterial disease.

Both tests were performed at the same session, the exercise test always preceding the hypoxia test. When the former caused changes in the ECG the latter was delayed until the tracing returned to its initial form. Otherwise a 5-minute interval was deemed enough.

The three standard limb leads were recorded, together with V2, V3, and V4, and with D2 or VR as a control. The frequency of occurrence of those types of abnormality which are regarded by various authorities as indicative of coronary disease was as follows. (1) Depression of RS–T segment by more than 0·5 mm. in one or more leads occurred on exercise in 28% of Group A, 61% of Group B, and 78% of Group C, and with hypoxia in 22%, 68·5%, and 61% respectively. (2) Increase in voltage of the T wave by more than 50% occurred on exercise in 20% of Group A, 46% of Group B, and 40% of Group C, and with hypoxia in 8·6%, 61%, and 53% respectively. (3) A change in form of the T wave occurred on exercise in 8% of Group A, 38% of Group B, and 30% of Group C, and with hypoxia in *nil*, 32%, and 47·7% respectively. When exercise caused a change in form of the T wave it often caused RS–T depression as well. One or both of these changes occurred with exercise in 44% of Group A, 69% of Group B, and 85% of Group C, and with hypoxia in 26%, 77%, and 95·4% respectively. [The above results are given as percentages only, despite the small numbers of cases studied.] (4) The appearance of significant arrhythmias as a result of either test was rare. Extrasystoles occurred on exercise in only 3 cases, all in Group C, and with hypoxia in only one case in Group B and 3 in Group C. *A. C. F. Green*

1363. **Exercise and Hypoxia Tests in Coronary Insufficiency. II. Physiopathological Significance and Diagnostic Value.** (Pruebas de esfuerzo e hipoxia en la insuficiencia coronaria. II. Valor fisiopatológico y valor diagnóstico)

J. E. DE LA PEÑA, G. RUBIO TREJO, M. ROMERO QUIROZ, and E. CABRERA COSÍO. *Archives del Instituto de cardiología de México* [*Arch. Inst. Cardiol. Méx.*] **27**, 540–562, Sept.–Oct., 1957. 5 figs., 25 refs.

Of the many types of test devised for the diagnosis of coronary insufficiency, those concerned with observation of the effects of exercise and hypoxia give the best results. The authors here discuss the practical application and diagnostic value of these tests in the light of the observations reported in their previous paper [see Abstract 1362]. The exercise test is simple and easy to carry out. It rarely causes precordial pain, the reactions being usually limited to tachycardia, elevation of the blood pressure, and tachypnoea. Opinions differ, however, as to the interpretation of the results and the reliability of the test. False positive results may be obtained in cases without coronary insufficiency, the factors contributing to their causation including thyroid disease, gastric distension, emotion, severe hyperventilation, upper respiratory tract infection, and the ingestion of alcohol or ephedrine. The hypoxia test is widely regarded as of positive value in the diagnosis of coronary insufficiency, yet it is far from being specific, since false positive results may occur and a negative result does not absolutely exclude coronary disease. In the opinion of most authors the results given by the two types of test are very similar, but whereas exercise tests are easier to perform, hypoxia tests are safer. On the other hand an exercise test may be impracticable for elderly invalids or patients with intermittent claudication or severe arthritis.

The present authors stress the need for simplicity both in the performance and in the interpretation of these tests. The most frequent electrocardiographic changes observed are RS–T depression, increased voltage of the T wave, and alteration of its form. Sometimes more than one of these features may be seen, though not necessarily in the same lead, and although none of them is diagnostic in itself, the absence of all three is unlikely in the presence of coronary disease, while the occurrence together of the first and third is equally unlikely in its absence. In agreement with other authors they regard the use of the standard limb leads as unnecessary, relying exclusively on leads V3, 4, and 5. This simplifies testing without significantly reducing the number of positive findings. Moreover, it reduces the chance of missing fleeting changes which are more likely to be shown in the more sensitive chest leads than in the limb leads. On the other hand they differ from other authors in regarding the development of precordial pain during a test as a positive finding.

In general they consider that tests of this type lack the high diagnostic value that has sometimes been accorded to them, and that the study of the electrocardiographic changes caused by exercise or hypoxia should be used in conjunction with, *and subordinated to*, the careful study of the clinical picture in the diagnosis of coronary arterial disease. *A. C. F. Green*

1364. **Choline in the Treatment of Patients with Coronary Atherosclerosis.** (Применение холина у больных коронарным атеросклерозом)

P. M. SAVENKOV. *Советская Медицина* [*Sovetsk. Med.*] **21**, 13–19, No. 8, Aug., 1957. 6 figs.

It has been shown that the ratio of the lecithin to the cholesterol level in serum is an index of the liability to atherosclerosis, a fall in this ratio being associated with an increase in level of the β lipoproteins, which carry the bulk of the cholesterol of the blood, and vice versa. The influence of choline in causing a rise in this ratio has been disputed by several observers, while others have claimed that it has a beneficial effect on experimentally induced atherosclerosis. The present author reports the effect of choline treatment on 68 patients (27 men and 41 women) with coronary atherosclerosis to whom 200 ml. of a 1% choline hydrochloride solution in 5% glucose was administered intravenously daily for 20 days at the rate of 30 to 40 drops a minute, while 5 ml. of a 20% solution was given orally three times a day, each patient thus receiving 5 g. of choline daily or 100 g. over the whole course. Another group of similar patients were given 6 g. daily by mouth only. All were maintained on a diet containing 50 g. of fat, 100 g. of protein, and 400 g. of carbohydrate. The blood lecithin and cholesterol levels were estimated before treatment, on the 11th day of treatment, and at the end of the course. In 26 cases the serum lipoproteins were estimated electrophoretically.

In 53 of the 68 cases the serum cholesterol level fell (mean 40 mg. per 100 ml.) and in 61 the lecithin level

rose (mean 53 mg. per 100 ml.); in 64 cases the lecithin: cholesterol ratio rose. Of the 26 cases in which the serum was examined by electrophoresis, the serum β-lipoprotein level fell in 20 (average fall 4·5%), while the α-lipoprotein level rose. The general condition of the patients improved greatly with treatment, their spirits rose, they slept better, and in many precordial pain diminished. In 6 cases the patients have remained under observation while taking choline continuously or at intervals for periods varying from 4½ months to 2½ years. Unpleasant side-effects, which occurred more often if intravenous choline was administered more rapidly than 40 drops a minute, included facial hyperaemia, sweating, and excessive salivation. *L. Firman-Edwards*

1365. **Vitamin B_{12} and Folic Acid in the Treatment of Coronary Atherosclerosis.** (Применение витамина B_{12} и фолиевой кислоты у больных коронарным атеросклерозом)
V. I. Bobkova. *Советская Медицина* [*Sovetsk. Med.*] **21**, 20–29, No. 8, Aug., 1957. 6 figs., 13 refs.

In view of reports in the literature of the beneficial effect of vitamin B_{12} (cyanocobalamin) and folic acid on fatty infiltration of the liver the author has tried these substances in the treatment of 49 patients (37 men and 12 women) with atherosclerosis of the coronary arteries, 18 patients receiving 20 μg. of vitamin B_{12} daily by intramuscular injection, 10 being given 30 mg. of folic acid orally twice daily, and 21 combined treatment with both substances.

In 14 out of the 18 patients treated with cyanocobalamin alone the blood cholesterol level fell in varying degrees, while in 16 the blood lecithin level increased at the end of 10 days' treatment. In 7 out of the 10 patients receiving folic acid alone the blood cholesterol level fell, and in 8 there was a rise in the blood lecithin content. Of the 21 patients receiving the combined treatment, all showed a fall in the blood cholesterol level and 17 a rise in the lecithin level; in 19 cases the lecithin: cholesterol ratio rose above unity. Combined treatment was therefore considered to be more effective than the use of either medicament alone. The attacks of precordial pain were abolished in 5 cases, while in 11 they diminished in frequency. *L. Firman-Edwards*

1366. **Effect of Sitosterol on the Concentration of Serum Lipids in Patients with Coronary Atherosclerosis**
F. P. Riley and A. Steiner. *Circulation* [*Circulation*] **16**, 723–729, Nov., 1957. 2 figs., 12 refs.

A colloidal suspension containing from 19 to 52·5 g. per day of β- and dihydro-β-sitosterol was administered orally to 13 patients with coronary atherosclerosis, 3 of whom had associated xanthomatosis. The serum total cholesterol concentration decreased during the 1- to 6-month periods of sitosterol ingestion. However, in only 9 of 18 instances of sitosterol administration in the 10 patients with coronary atherosclerosis was this fall in serum cholesterol statistically significant. In the 3 patients with xanthomatosis and coronary atherosclerosis, the serum cholesterol level fell significantly but rebounded toward control values after 6 to 9 weeks, despite the maintenance of the sitosterol regimen. The fall in mean serum total cholesterol during sitosterol feeding was more impressive in this latter group in which the initial serum total cholesterol values were higher. The effect on the neutral fat and total lipid levels of the serum was variable. The cholesterol: phospholipid ratio tended to remain unchanged throughout the study. Results obtained in this clinical study indicate that further observations are necessary in order to demonstrate that the fall in serum cholesterol coincident with sitosterol ingestion is greater than the fluctuation of the serum cholesterol levels that occur in patients with coronary atherosclerosis.—[Authors' summary.]

HYPERTENSION

1367. **Overweight and Hypertension.** [In English]
T. Bjerkedal. *Acta medica Scandinavica* [*Acta med. scand.*] **159**, 13–26, Oct. 30, 1957. 6 figs., 17 refs.

The relationship between overweight and hypertension was studied at the Institute of Hygiene, University of Oslo, and for this purpose the auscultatory blood-pressure readings obtained during periodic health examinations of 14,784 employees in 112 different Norwegian industrial plants were analysed in relation to age, sex, height, and weight. A steady rise in the average systolic and diastolic pressure values with increasing body weight was observed in all age groups. A comparison of the percentage distribution according to blood pressure of subjects of the same age in the three groups, underweight, normal weight, and overweight, indicated that in all of them there was a small increase in pressure with increasing weight, there being no preponderance of subjects with high blood pressure among the obese. The author suggests that such an over-all increase in blood pressure with weight can be explained on the basis of the established observation that in subjects with large arms a falsely high blood pressure reading is obtained when the indirect (auscultatory) method of measurement is used. He does not consider that there is any evidence of a real relationship between obesity and hypertension. *P. Hugh-Jones*

1368. **Arteriosclerosis and Renal Hypertension. Indications for Aortography in Hypertensive Patients and Results of Surgical Treatment of Obstructive Lesions of Renal Artery**
E. F. Poutasse and H. P. Dustan. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **165**, 1521–1525, Nov. 23, 1957. 1 fig., 17 refs.

In the 2-year period 1955–56, at the Cleveland Clinic Foundation, Cleveland, Ohio, 104 patients with hypertension were subjected to translumbar aortography. The authors consider that this procedure is indicated only in the following 4 groups of patients: (1) those with unexplained inequality of size or function of the kidneys as shown by intravenous pyelography; (2) young patients without a family history of, or obvious cause for, hypertension; (3) patients over 55 years of age who suddenly develop malignant hypertension; and (4) patients of any

age with essential hypertension which suddenly becomes more severe (particularly if initiated by flank pain suggestive of renal infarction). Of the 104 patients, who were selected on this basis, 30 were found to have focal disease of the renal artery (arteriosclerotic plaques, unilateral in 17 and bilateral in 6; fibrous intimal stenosis, unilateral in 1 and bilateral in 1; renal arterial embolism, 1; renal arterial thrombosis, 1; renal arteriosclerosis associated with chronic pyelonephritis, unilateral in 2 and bilateral in 1). Surgery (nephrectomy, renal arterial graft, or endarterectomy) was performed in 19 cases. In 11 of these blood pressure became normal and in 6 the fall in blood pressure was satisfactory, although it did not reach normal; there were 2 deaths, one from renal failure and one from haemorrhage.

K. G. Lowe

BLOOD VESSELS

1369. **General Hemodynamics and Splanchnic Circulation in Patients with Coarctation of the Aorta**
J. W. CULBERTSON, J. W. ECKSTEIN, W. M. KIRKENDALL, and G. N. BEDELL. *Journal of Clinical Investigation* [*J. clin. Invest.*] **36**, 1537–1545, Nov., 1957. 1 fig., 46 refs.

A general haemodynamic study of 10 patients with coarctation of the aorta is reported from the Cardiovascular Research Laboratories of the College of Medicine of the State University of Iowa. In contrast to findings in cases of essential hypertension and renal hypertension, no generalized increase in peripheral resistance was found. The hypertension in the upper arterial compartment in cases of coarctation of the aorta is related, it appears, to the degree of narrowing, to the foreshortening of the aortic compression chamber, and to the increased stroke volume of the left ventricle. No evidence of renal or hepatic ischaemia was obtained. Hepatic blood flow was estimated in 5 cases and was found to be well above the normal average. Oxygen consumption in the splanchnic circulation was generally parallel with the hepatic blood flow, but was not reduced in any of the 4 cases in which it was estimated.

A. I. Suchett-Kaye

1370. **Serum Lipid Levels in Normal Persons. Findings of a Cooperative Study of Lipoproteins and Atherosclerosis**
L. A. LEWIS, F. OLMSTED, I. H. PAGE, E. Y. LAWRY, G. V. MANN, F. J. STARE, M. HANIG, M. A. LAUFFER, T. GORDON, and F. E. MOORE. *Circulation* [*Circulation*] **16**, 227–245, Aug., 1957. 13 figs., 13 refs.

Measurements of S_f 12–20, S_f 20–100, and total serum cholesterol made on 10,690 men and 3,404 women are reported and the relation of lipid level to race, source, age, sex, blood pressure, and weight is described. Distributions for men 40 to 59 are reported in detail. The groups studied, while not selected as representative of the population at large, were remarkably similar in their lipid levels. The lipid levels of only 2 of the 33 [population] groups differed significantly from the average. No convincing explanation for either of these exceptions was discovered. The data in this study were mainly from a white population. Data for nonwhites came primarily from 2 aberrant groups and were too meager to allow a clear characterization of lipid levels. The levels for nonwhites from these 2 sources were closer to those of the white members of these groups than to the levels of the general population.

Cholesterol levels for men and women were found to be about the same at age 20. For both sexes the level rises with age but at first the rise is much greater for men than women. Above age 50, however, the level is higher for women than men and the level for women continues to rise after that age—at least within the age series for this study. The level for men reaches a peak at age 55, after which it declines. The relation of age and sex with lipid level for S_f 12–20 and S_f 20–100 appeared to be similar to that for cholesterol.

Correlations of lipid levels with blood pressure and weight were positive but very low. Hypertension of obesity, however, is associated with some elevation of lipid levels. S^f 20–100 was found to be the most sensitive of the 3 lipid measures to sex and race differences. In the age group 40 to 59 it was the only one that exhibited a definite race and sex differential. In addition, it had the highest correlation with weight and with blood pressure.—[Authors' summary.]

1371. **Clinical Experience with the Anticoagulant Acenocoumarin (" Sintrom ")**
F. ALEXANDER, J. L. KOPPEL, P. M. ARSCOTT, and J. H. OLWIN. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 558–564, Oct., 1957. 7 figs., 17 refs.

Acenocoumarin (" sintrom ") was administered to 90 patients both with and without thromboembolic disease. Acenocoumarin was found to be an effective and safe prothrombin depressant, therapeutic levels of prothrombin being attained, on the average, within 5 days, with some individual induction periods being as short as 12 hours. Following withdrawal of the drug, prothrombin rises in most instances to above 30% of normal within 36 hours. Eighty per cent prothrombin levels are attained in 6 to 7 days, and pretherapy levels, within 12 days. The rate of recovery is hastened by the oral or intravenous administration of water-soluble or fat-soluble vitamin-K-active preparations.

In addition to its effect on prothrombin, acenocoumarin was observed to depress the levels of Factor VII, Ac globulin, and autoprothrombin II. The TAMe (*p*-toluenesulfonyl-l-arginine methyl ester) assay for prothrombin was found to be well suited as a means for controlling administration of acenocoumarin.

Liver function tests and bone marrow biopsies gave no evidence of toxic effects. In the 90 patients studied bleeding was observed in only one instance. This was present as gross hematuria and occurred while the prothrombin was within the control bracket; it was attributed to a urethritis.—[Authors' summary.]

Correction. February issue, Abstract No. 357: The investigations reported were carried out on 58 subjects, not 2 as stated. In the 7th line from the end for the word "meal" read "plasma".—EDITOR

Clinical Haematology

1372. **Intracranial Complication of Leukemia in Children**
M. P. SULLIVAN. *Pediatrics* [*Pediatrics*] **20**, 757–781, Nov., 1957. 11 figs., 28 refs.

Attention is drawn to the increased incidence of manifestations of cerebral complications in children with acute leukaemia since the introduction of treatment with steroids and chemotherapeutic drugs. Symptoms may occur at a time when the blood picture indicates remission and are related principally to manifestations of increased intracranial pressure. In this paper from the M. D. Anderson Hospital and Tumour Institute, Houston, Texas, 7 cases are described in detail. The occurrence of cerebral complications was not related to the type of treatment given; necropsy revealed involvement of the pituitary gland and capsule, the choroid plexus, and the meninges respectively in 3 different cases.

The possibility that cerebral lesions represent local mesenchymal overgrowth rather than metastatic disease is discussed. Reference is made to the finding of other workers that the antimetabolites reach the intrathecal space in low concentrations only. The author states that the most effective treatment at the present time is x-irradiation of the entire skull, 250 to 500 r. being given in 7 to 10 days. *Mary D. Smith*

1373. **Treatment of Severe Haemorrhage**
P. FIRT and L. HEJHAL. *Lancet* [*Lancet*] **2**, 1132–1137, Dec. 7, 1957. 11 figs., bibliography.

The authors report, from the Institute for Clinical and Experimental Surgery, University of Prague, the main results of an extensive experimental investigation on over 500 dogs of the effects of massive transfusion of citrated and of heparinized blood which was undertaken in order to elucidate the occurrence of cardiac failure in patients receiving blood transfusions apparently adequate in respect of total amount and rate of transfusion. In most of the experiments the dogs were bled at a slow rate until the arterial blood pressure fell to 60 mm. Hg.

In all, 9 different experiments were performed, with the following results. (1) Of 8 dogs given a transfusion of their own heparinized blood, none showed signs of cardiac overloading and all survived. (2) Of 8 similar dogs transfused with their own citrated blood, all showed cardiac overloading or failure and all died. (3) Very rapid transfusion with heparinized blood at rates varying from 20 to 77 ml. per kg. body weight per minute produced no untoward results. (4) The injection of 3·8% citrate into the jugular vein caused arterial pressures to fall and then rise and venous pressures to rise and then fall. (5) The injection of 0·7 ml. of 10% calcium gluconate or 0·5 ml. of 1% procaine per kg. body weight completely counteracted the effect of the injection of 3·8% citrate. The remaining experiments were concerned with the transfusion of citrated or heparinized blood into either an artery or a vein and at varying rates.

From one of the graphs accompanying the paper it can be seen that pulmonary arterial pressure after transfusion of citrated blood remained high, even after the venous pressures had returned to normal, owing to the pulmonary vasoconstrictive effect of citrate. But citrate in larger doses had a direct depressant effect on the myocardium which was the more marked, the more shocked or anaemic the dog was before transfusion. In these conditions relatively small amounts of citrate may be dangerous. The authors suggest that the apparently beneficial effect of intra-arterial transfusion results from the clearance of citrate from the blood in the capillary bed so that a smaller amount of citrate reaches the pulmonary bed and the coronary arteries. As the intravenous route of transfusion is much more convenient and easier to start, and as the harmful effect of citrate can, as shown, be counteracted, there appears to be no further indication for intra-arterial transfusion except in cases of cardiac standstill with clinical death. In all other conditions intravenous transfusion may be used.

In the last part of the paper some clinical results are presented and 3 illustrative cases are briefly described. The suggested technique is to give 10 ml. of 10% calcium gluconate before transfusion at rates up to 6 ml. per kg. per minute (about 400 to 500 ml. per minute), with a further 15 ml. of calcium gluconate intravenously after the first 100 ml. of blood has been run in; in larger transfusions 10 ml. of 10% calcium gluconate should be given for every 500 ml. of blood. For plasma transfusion a larger amount of calcium is suggested together with 0·6 ml. of 0·25% solution of procaine per kg. before transfusion and then as a continuous drip at the rate of 5 drops per minute per 10 kg. body weight. The calcium solution must, of course, never be given in the same drip or into the same vein as the blood. *F. Hillman*

1374. **The Natural History of Homozygous Sickle-cell Anaemia in Central Africa**
H. C. TROWELL, A. B. RAPER, and H. F. WELBOURN. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **26**, 401–422, Oct., 1957. 2 figs., 36 refs.

The authors present a detailed account of the clinical features of 59 cases of homozygous sickle-cell anaemia in persons of pure African descent investigated at Mulago Hospital, Kampala, Uganda. No case was accepted for study until haemolytic anaemia had been demonstrated and electrophoresis of the haemoglobin (Hb) by the "hanging-strip" method in veronal buffer at *p*H 8·6 had shown a single band in the position of Hb–S. In very small infants, in whom considerable amounts of Hb–F are retained, the final diagnosis was deferred until the characteristic pattern had been obtained. No determination of Hb–D was made, since this anomaly has not so far been recorded in the population concerned.

The disease, which is initially mild, appears in the majority of cases in the first 3 months of life, and severe

symptoms develop after the age of 6 months, the anaemia increasing and being accompanied by episodes of fever, pain and swelling of the hands and feet, jaundice, and enlargement of the liver and spleen. The authors stress the frequent finding of osteopathy, which occurred in 11 out of 19 children aged 6 to 24 months. In later childhood the disease tends to be less severe, while in adolescence its effects are seen in the characteristic physique, consisting in long, thin limbs, an asthenic build, and poorly developed secondary sex characteristics. Adult sufferers from sickle-cell anaemia are extremely rare in Uganda. In the present series there were 11 known deaths, 6 of them occurring in patients under the age of 24 months and the other 5 in the age group 2 to 12 years. The post-mortem findings in 5 cases are described. In infancy, however, there are few post-mortem morbid appearances, the characteristic siderofibrosis of the spleen developing about the age of 5 years, and thereafter the non-specific changes of any haemolytic anaemia are seen.

The present study revealed important differences between the disease as seen in Uganda and the disease in West Africa and the Americas, notably in the earlier age of onset, the more rapid development, the higher mortality, the frequency of bony swellings, and the rarity of thrombotic, renal, and neurological complications and of leg ulcers in Uganda. The authors suggest that some of these differences may be explained by the absence of haemoglobin variants in Central Africa, a state of affairs which tends to produce a severe form of the disease and early death, so that the complications, which in the " classic " form of the disease usually appear in adolescence or later, are not seen. *D. G. Adamson*

1375. **Response of Megaloblastic Anaemia to Prednisolone** A. Doig, R. H. Girdwood, J. J. R. Duthie, and J. D. E. Knox. *Lancet* [*Lancet*] **2**, 966–972, Nov. 16, 1957. 4 figs., 16 refs.

The unexpected haematological response of megaloblastic anaemia in a patient who was being treated with prednisolone for her rheumatoid arthritis led the authors to use this drug in 8 further cases at the Northern General Hospital, Edinburgh,in doses of 30 mg. per day, administered orally. Of these 8 additional patients, 2 had Addisonian pernicious anaemia, one pernicious anaemia and rheumatoid arthritis, 2 coeliac disease persisting into adult life, and in one the megaloblastic anaemia followed partial gastrectomy; the other 2 patients had megaloblastic anaemia associated with long-standing rheumatoid arthritis. These cases are distinguished from the classic Addisonian pernicious anaemia by showing consistently low serum levels of cyanocobalamin (vitamin B_{12}) but, as shown by isotope studies, the absorption of the vitamin is within (although towards the lower limit of) the normal range. Gastric juice from these patients caused some improvement in the absorption of cyanocobalamin when tested on cases of true Addisonian pernicious anaemia, " suggesting intrinsic factor activity ". It is considered likely that the rheumatoid disease was in some way responsible for the development of the cyanocobalamin deficiency. In 8 of the 9 patients a haematological remission was obtained, with reversion of erythropoiesis from megaloblastic to normoblastic. The responses were rather slow and suboptimal, but occurred in cases both of cyanocobalamin and of folic acid deficiency, showing that the effect of prednisolone is not due to intrinsic-factor-like activity. The fall in the serum iron level within 48 hours of administration of specific haematinics did not occur in these cases. In the 9th case the absence of response was attributed to the short duration of treatment with prednisolone—6 days instead of 20 or more. It was shown by assay with *Streptococcus faecalis* and *Lactobacillus leichmannii* that the prednisolone used contained no folic or folinic acid or cyanocobalamin and that there was no significant change in the patients' serum cyanocobalamin level during prednisolone administration.

The authors are very careful to point out that these observations are of theoretical interest only, and stress that they do not recommend prednisolone for the treatment of megaloblastic anaemia. Moreover, they consider that such treatment may possibly precipitate neurological involvement, as was thought to have occurred in one of their patients. They also point out the danger of giving prednisolone in cases of rheumatoid and other disease, as such treatment may mask an associated or related megaloblastic anaemia. No explanation of this action of prednisolone can at present be suggested.

R. B. Thompson

1376. **Megaloblastic Anemia in " Alcoholic " Cirrhosis** S. E. Krasnow, J. R. Walsh, H. J. Zimmerman, and P. Heller. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 870–880, Dec., 1957. 7 figs., 30 refs.

Over the 4-year period 1953–6 a total of 350 histologically proved cases of hepatic cirrhosis were observed. Examination of the bone marrow in the 96 patients who were anaemic revealed megaloblastosis in only 7 (2%). All 7 patients were alcohol addicts and were consuming a " grossly inadequate " diet. The dietary deficiencies, however, appeared to be no more severe than those of other non-anaemic cirrhotics and the degree of megaloblastic anaemia could not be correlated with the severity of the cirrhosis. In 5 cases there was free hydrochloric acid in the gastric juice and in 3 of these absorption of radioactive cyanocobalamin was normal. One patient who died from perforated duodenal ulcer was presumed to have had normal gastric acidity and another died before gastric acidity could be determined. Of the 5 surviving patients, 3 improved with dietary measures alone, but 2 were so anaemic that more immediately effective treatment was required. The authors conclude that megaloblastosis is the result of a combination of factors. *R. B. Thompson*

1377. **Endogenous Formation of Carbon Monoxide in Hemolytic Disease. With Special Regard to Quantitative Comparisons to Other Hemolytic Indices.** [In English] L. Engstedt. *Acta medica Scandinavica* [*Acta med. scand.*] **159**, Suppl. 332, 1–61, 1957. 12 figs., bibliography.

Respiratory System

1378. **Prophylactic Use of Oxytetracycline for Exacerbations of Chronic Bronchitis**
P. C. Elmes, C. M. Fletcher, and A. A. C. Dutton. *British Medical Journal* [*Brit. med. J.*] **2**, 1272–1275, Nov. 30, 1957. 1 fig., 12 refs.

A controlled trial of the effect of short courses of oxytetracycline on exacerbations of chronic bronchitis in 88 affected subjects in regular employment is reported from the Postgraduate Medical School of London, 44 subjects being given 1 g. of oxytetracycline daily for 5 days at the onset of an exacerbation and 44 being given tablets containing lactose. The subjects in the oxytetracycline group lost half as much time from work with each exacerbation as did the group given a placebo, but the figure was not statistically significant. Exacerbations in both the oxytetracycline and the placebo groups were significantly shorter in duration than those in subjects given no tablets of any kind. *Streptococcus pneumoniae* and *Haemophilus influenzae* were the only pathogenic organisms isolated from the sputum of patients throughout the trial, but the presence or absence of these organisms did not affect the duration of the exacerbations. No resistant strain of these pathogens was isolated even after several courses of oxytetracycline.

Although the figures did not show a significant difference by statistical standards between the two groups, the authors nevertheless consider that oxytetracycline is effective in the treatment of exacerbations of chronic bronchitis. *G. M. Little*

1379. **An Evaluation of Sputum Examination in Chronic Bronchitis**
W. Brumfitt, M. L. N. Willoughby, and L. L. Bromley. *Lancet* [*Lancet*] **2**, 1306–1309, Dec. 28, 1957. 4 figs., 20 refs.

It is well known that sputum may be contaminated with organisms from the upper respiratory tract and that bacteriological examination often yields unreliable results. To overcome these difficulties the authors, at St. Mary's Hospital, London, have devised a method of direct swabbing of the bronchial mucosa through a bronchoscope by means of a polythene swab-carrier to the end of which is attached a small metal cup which protects the swab during its passage to and from the bronchial tree. Sputum, bronchial swabs, and throat swabs from 42 patients without respiratory disease and 27 with chronic lower respiratory tract infection were cultured simultaneously. Bronchial swabs from the non-infected group were always sterile, but sputum specimens and throat cultures from the same group yielded organisms which are frequently regarded as pathogenic. In the infected group *Haemophilus influenzae*, pneumococci, coliform bacilli, and streptococci were commonly cultured from bronchial swabs, the same organisms being found in the sputum in all except 2 cases. There was much closer correlation between bronchial-swab and sputum cultures when the throat was not contaminated with additional organisms.

[The authors' findings are in close accord with those of previous studies on the bacteriology of infected sputum.] *Paul B. Woolley*

1380. **Long-continued Treatment with Tetracycline and Prednisolone in Chronic Bronchitis. A Controlled Trial**
E. N. Moyes and R. A. Kershaw. *Lancet* [*Lancet*] **2**, 1187–1191, Dec. 14, 1957. 17 refs.

In this study of the value of tetracycline and prednisolone in the treatment of chronic bronchitis, which was carried out at the Royal Infirmary, Worcester, 90 patients were selected from among those attending the chest clinic between November 5, 1956, and January 10, 1957. Chronic bronchitis was defined as a condition causing a productive cough, usually with dyspnoea and bronchospasm, which had been present for 2 years or longer. Patients with asthma, cardiac failure (past or present), hypertension, peptic ulcer, or mental instability were excluded from the trial, while only those with moderate or severe disability from the bronchitis were included. The 90 patients, 81 male and 9 female, ranged in age from 20 to 67 (mean 53) and they were allocated to one of three treatment groups by a system of random selection. The trial, which lasted for 4 months, was completed by 86 of the 90 patients, and the treatment in the three groups was as follows: Group A (the control group, containing 31 patients) was given 2 dummy tablets 3 times a day for 7 days, then one 3 times a day, together with 0·1 g. of aminophylline 3 times a day. Group B (27 patients) received tetracycline, 500 mg. 3 times a day for 7 days, then 250 mg. 3 times a day, with aminophylline as above. Group C (28 patients) were treated with tetracycline as in Group B plus prednisolone, 5 mg. 3 times a day. The dummy tablets resembled those of tetracycline in size and colour, and the aminophyline tablets resembled those of prednisolone. At monthly intervals a record was made of the daily volume and purulence of the sputum, the number of head colds, the incidence of acute exacerbations and number of days ill or off work, the degree of dyspnoea and bronchospasm, the vital capacity (54 cases), side-effects of the treatment, and the patient's and physician's opinion of the progress. The sputum was examined bacteriologically at the beginning and the end of the trial.

The results were as follows. Of the 31 control patients in Group A, 2 felt better, 26 were unchanged, and 3 were worse; of the 27 in Group B, 16 were better, 9 unchanged, and 2 worse; while of the 28 in Group C, 17 were better, 10 unchanged, and one worse. Thus more than half the patients in Groups B and C were improved, the severity of dyspnoea and bronchospasm and the number of acute exacerbations being reduced

in most patients in these groups, while the sputum was usually smaller in volume and less purulent by the end of the second week of treatment. *Staphylococcus pyogenes* was the commonest pathogen (38 cases) found in purulent specimens of sputum, while *Haemophilus influenzae* was found in 19 and pneumococci in 8. The addition of prednisolone did not appear to influence the results of treatment with tetracycline. Diarrhoea was the most important side-effect, being reported by 33 (60%) of the patients taking tetracycline, usually in the first week when the larger dose was being taken; it was mild in 19 cases, but bad enough in 14 to require reduction of the dosage. Diarrhoea, probably of nervous origin, also occurred in 12 (39%) of the controls, perhaps because the patients had been warned of this possible complication. The dose of prednisolone had to be reduced in 10 patients on account of side-effects. The authors conclude that long-continued treatment with tetracycline can be useful in chronic bronchitis, in which the sputum is usually purulent and in which there are acute exacerbations; on the other hand corticosteroids appear to be of little, if any, value in this condition.

Arthur Willcox

1381. **Bronchiectasis and Acute Pneumonia**

W. RUBERMAN, I. SHAUFFER, and T. BIONDO. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **76**, 761–769, Nov., 1957. 7 refs.

The incidence, diagnostic features, and stability of bronchiectasis as a sequel of recent pneumonic infection was studied at the U.S. Army Hospital, Fort Dix, New Jersey. Of 1,711 patients with acute pneumonia, 69 were selected for bronchography, iodized oil being administered endotracheally after preliminary bronchoscopy. Bronchiectasis was present in 29 of these 69 patients; in one further patient the bronchogram was abnormal initially and found to be normal on repeat examination. In the patients with bronchiectasis the mean duration of pneumonia was 2 months, compared with one month in patients without bronchiectasis. After all acute pneumonic manifestations had subsided persistent rales were noted in 22 of the former group and in 4 of the latter. Repeat bronchography in 14 of the patients with bronchiectasis revealed reversion to normal in only one.

B. Golberg

1382. **Pulmonary Sarcoidosis. A Physiopathologic Analysis**

F. D. GRAY and F. G. GRAY. *Journal of Chronic Diseases* [*J. chron. Dis.*] **6**, 572–580, Dec., 1957. 4 figs., 19 refs.

The results of a study of the relationship between pulmonary function and the pathological picture in 23 patients with pulmonary sarcoidosis are reported from Yale University. Residual lung volumes were calculated by subtracting the expiratory reserve volume from the functional residual capacity, the values obtained being compared with those for 67 healthy subjects and for patients with various other cardiopulmonary diseases. In the patients with sarcoidosis the average residual volume was low compared with the normal range of 0·46 to 2 litres and with the higher than normal range of 0·8 to 8 litres in the patients suffering from other cardiopulmonary diseases.

A study of 11 of the cases of sarcoid before and after inhalation of an aerosol of adrenaline showed that the residual volume increased in 7 cases and decreased in 3, together with an increase in maximum breathing capacity. This trend was contrary to the experience in other types of chronic lung disease. Observations on 9 patients during prolonged steroid therapy showed that there was an increase in maximum breathing capacity in 7 and a decrease in 2, whereas the residual lung volume increased in 6, decreased in 2, and was unchanged in one patient. The improvement brought about by adrenaline and adrenocortical steroids is considered to be due to their effect on the sarcoid inflammatory tissue.

D. Geraint James

1383. **Clinical Study of Pulmonary Distomiasis (Paragonimiosis).** (Клиника легочного дистомиаза (парагонимоза))

G. TERZIEV, B. ZOGRAFSKI, I. DRAČEV, D. MITROBA, and D. СВЕТКОВ. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **35**, 60–65, Dec., 1957. 6 refs.

This communication from the Pavlov Medical Institute, Plovdiv, Bulgaria, describes a clinical study of 150 cases of pulmonary distomiasis seen at a Bulgarian hospital in North Korea, of which 141 were in men and 9 in women; more than half the patients were between 14 and 25 years of age. In all cases the infection was due either to eating uncooked crabs or to drinking infected water from streams or wells. In one-third of the cases the condition was at first mistakenly diagnosed and treated as pulmonary tuberculosis. A correct diagnosis, however, was arrived at in every case on examination of the sputum, which invariably contained the ova of *Paragonimus westermani*. But even in the absence of eggs, the authors state, the diagnosis of distomiasis is practically certain when the sputum is found to contain erythrocytes, eosinophil leucocytes, and Charcot–Leyden crystals. The sputum may have a fishy smell and is usually of a rusty colour if it contains blood.

The course of the disease is relatively mild and the prognosis on the whole is good. In this series the patients were treated with emetine, given either alone intravenously, or in combination with sulphonamides or with penicillin introduced into the bronchi. Chinese workers have reported good results from the use of chloroquine in these cases.

A. Orley

1384. **The French Inquiry into the Aetiology of Broncho-pulmonary Cancer. The Role of Tobacco.** (L'enquête française sur l'étiologie du cancer broncho-pulmonaire. Rôle du tabac)

D. SCHWARTZ and P. F. DENOIX. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **33**, 3630–3643, Oct. 30, 1957. 7 refs.

Many attempts have been made in recent years to assess by statistical means the part played by tobacco in the aetiology of cancer of the lung. In the investigation reported in this paper from the Institut Gustave-

Roussy, Villejuif (Seine), the authors have attempted to study certain aspects of the problem which have not previously been dealt with. Thus a group of patients with cancer of the lung was compared not only with three different matched control groups—namely, patients with cancer of sites other than the respiratory or upper digestive tracts, patients with non-cancerous diseases, and patients admitted to hospital as the result of accidents —but also with a group of patients with cancer of sites other than the bronchus and lung which come in contact with tobacco or tobacco smoke, such as the mouth, pharynx, larynx, and oesophagus. (In addition, all the subjects were asked many questions about their social environment, antecedent history, and other matters which were not concerned with the use of tobacco, but this information is not dealt with in the present paper.) The main data were obtained retrospectively from patients who were already affected by the diseases studied. Each of the patients with lung cancer was matched, so far as possible, with patients in the other 4 groups of the same sex (all were men) and in the same 5-year age group drawn from the same hospital group during the same period, and all these patients were interrogated by the same investigator.

Altogether 602 patients with lung cancer were studied; 430 were matched with patients in each of the other 4 groups and 172 were matched only with patients in the groups suffering from non-cancerous disease and accidents. Comparison of the smoking habits of the two groups without cancer showed no appreciable differences between them. These groups were therefore combined and compared in turn with the other 3 groups. Patients with lung cancer were distinguished from them in that more were smokers, more smoked cigarettes and fewer pipes, their average consumption of cigarettes was higher, more inhaled, and fewer had given up smoking. Patients with cancer of other sites in the upper respiratory and digestive tracts showed similar but less marked differences, but there was no deficiency of pipe-smokers and no excess of inhalers. Patients with other types of cancer did not, as a group, show any appreciable differences in their smoking habits from patients without cancer.

Analyses were also made of the interrelations between the method of smoking, amount smoked, inhalation, and cessation from smoking in the data from the 602 patients with lung cancer and the 1,204 without cancer. These showed that the risk of developing lung cancer increased with the number of cigarettes smoked, but not with the amount of tobacco smoked in a pipe, while for the same consumption of cigarettes the risk was lower among men who smoked a pipe as well. The proportion of men who inhaled was greater among cigarette smokers than among those who smoked both cigarettes and a pipe, and was greater among the latter than among men who smoked a pipe only; these differences would explain some (though not all) of the differences between the risks for the different types of smoker. More of the men who smoked heavily inhaled than of those who smoked lightly, but the risk was greater for inhalers at each level of smoking. The tendency to give up smoking cigarettes and the age at stopping were unrelated to the daily amount smoked, and it appeared that the risk of developing lung cancer increased progressively with the age of stopping smoking.

Richard Doll

1385. **A History of Pulmonary Resection**
G. E. Lindskog. *Yale Journal of Biology and Medicine* [*Yale J. Biol. Med.*] **30**, 187–200, Dec., 1957. 47 refs.

1386. **Extra-pulmonary Bronchogenic Cysts of the Mediastinum.** (Бронхогенные внелегочные кисты средостения)
T. P. Makarenko and M. D. Rjapolova. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **38**, 69–75, No. 11, Nov., 1957. 3 figs., 7 refs.

Bronchogenic cysts may be congenital or acquired; congenital cysts arising from the lung may be subdivided into those of bronchogenic and those of alveolar origin, while acquired cysts are usually the result of trauma. Examples are here given, with full case notes, of (1) a traumatic bronchogenic cyst which developed, following a war injury, in the left pleural cavity; (2) an air-containing cyst located in the anterior mediastinum; and (3) a cyst in the posterior mediastinum. The patients, 2 men and one woman, were aged 30, 32, and 40 respectively.

The clinical signs produced by these cysts vary much with their location, the stage of development, and the presence or absence of a communication with a bronchus. In the early stages they may present few symptoms, but as they grow they cause pressure on neighbouring structures, and if they become infected or if their communication with the bronchus becomes obstructed the symptoms may become grave, necessitating urgent surgical intervention. The commonest symptoms are a sensation of pressure in the chest, pain, progressive dyspnoea, cough, fatigue, and sometimes dysphagia. The contents of the cyst consist of air and fluid, often mixed with altered blood and even pus. In one of the authors' cases a large, opaque, round shadow was seen in the radiograph, and shortly afterwards the patient suddenly coughed up 700 ml. of a thick, coffee-coloured fluid, and was then much relieved. A further radiograph now showed the cyst to be much smaller, but containing a large air-bubble with a horizontal fluid level. This cyst, and that in the anterior mediastinum of the second patient, were successfully removed by the senior author. In the third case the cyst was in the posterior mediastinum, contained purulent fluid, and was in close relation to the inferior vena cava. At operation removal was found to be impossible; the symptoms recurred 2 years later, but further operation was refused.

The differential diagnosis of such cysts is from echinococcal cysts, dermoids, lung abscess, encysted empyema, and pneumothorax. Serial radiographs are of great value in diagnosis; these may show that the cyst varies in size from time to time if there is a communication with the bronchus, and the presence of air or of a fluid level is strongly suggestive of a cyst of bronchogenic origin. Bronchography may also be of help. The only treatment is surgical removal of the cyst with ligation of the bronchial connexion.

L. Firman-Edwards

Otorhinolaryngology

1387. **Congenital Microtia and Meatal Atresia. Observations and Aspects of Treatment**
Y. MEURMAN. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **66**, 443–463, Oct., 1957. 5 figs., 18 refs.

The author describes a series of 74 cases of congenital microtia and meatal atresia seen at the University Otolaryngological Clinic, Helsinki, during a period of 6 years, with particular reference to the radiographic appearances. The cases are divided into three grades according to the classification used by Marx and also by Altmann. In Grade I (24 cases) there is a malformed auricle which shows most of the characteristic features, but is smaller than that of the unaffected ear. Included in this group are a few cases with a normal pinna but an absent canal. In Grade II (45 cases) there is a rudimentary auricle, with atresia of the canal. In Gradė III (5 cases) the deformity of the auricle is much greater, there being sometimes only a malformed lobule. There is a rough inverse relationship between the degree of microtia and the extent of pneumatization of the mastoid process, which is notably retarded in Grade–III cases, and of development of the attic. There seems to be no significant correlation between ossicular deformity and cell development.

Deafness in the author's cases was usually of the middle-ear type and of moderate severity (about 50 to 60 db. over the speech range). From the point of view of improvement of hearing, the results of operation have been disappointing. The difficulties are great, and there is always a risk of damaging the facial nerve or the labyrinth. The greatest obstacle to fenestration lies in the difficulty of identification of the horizontal canal, and in the author's opinion the attempt should be made only in special cases. There was no real evidence of a hereditary influence in most of his cases.

F. W. Watkyn-Thomas

1388. **Stapes Mobilization in Otosclerosis**
Y. MEURMAN. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **66**, 464–479, Oct., 1957. 4 figs., 20 refs.

Up to the end of 1956 the author had carried out mobilization of the stapes in 379 cases of otosclerosis at the University Otolaryngological Clinic, Helsinki. He has abandoned the original technique of Rosen, which in his opinion does not give adquate exposure, and performs a much more extensive operation involving removal of a large part of the postero-superior meatal wall. Atticotomy does not, in the author's experience, appear to be necessary.

He makes his attack on the ossified annular ligament of the stapes, mobilizing it by division of the bony outgrowths, a method which he has found more effective than that used by Rosen or the modifications suggested by Myerson and Goodhill, who loosen the stapes by mechanical vibration. He has never deliberately fractured the anterior crus and foot-piece, as suggested by Fowler and Altmann, but where this has occurred accidentally good primary improvement has been obtained. When the stapes becomes fixed again after operation remobilization is successful in about two-thirds of cases. He makes no exaggerated claims for the operation, but is convinced that it is usually worth a trial before fenestration is resorted to.

F. W. Watkyn-Thomas

1389. **Mobilization of the Stapes in Otosclerosis by a Transtympanic Technique**
L. W. ALEXANDER. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **66**, 383–390, Oct., 1957. 5 figs., 5 refs.

The author describes his experience of mobilization of the stapes in some 75 cases of otosclerosis, the indications for operation being those laid down by Kos (*J. Amer. med. Ass.*, 1957, **163**, 814). He adheres to Rosen's original method, with removal of the supero-posterior portion of the bony annulus and exposure of the processus gracilis, the head and neck of the stapes as well as its foot-piece, the entire length of the stapedius tendon, and the chorda tympani nerve. He dislikes any direct attack on the foot-piece, which may produce labyrinthitis. Although he states that in his experience postoperative complications are " not common ", he mentions labyrinthitis, facial paralysis, middle-ear suppuration, and perforation of the tympanic membrane as being amongst those he has encountered. " Satisfactory to excellent " results were obtained in about 40% of cases.

F. W. Watkyn-Thomas

1390. **Intravascular Agglutination of the Blood. Major Factor in Otosclerosis, Ménière's Disease, Tinnitus, Vertigo; Neural Deafness—Total, Partial, Transitory, Recurrent, Progressive**
E. P. FOWLER. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **66**, 408–413, Oct., 1957. 3 figs., 9 refs.

On the basis of his observations over the past 10 years the author asserts that anoxia is the determining factor in the pathogenesis of otosclerosis, Ménière's disease, tinnitus, vertigo, and nerve deafness, the anoxia being produced by the " sludging ", or intravascular agglutination, of erythrocytes. Such " sludging " is produced by a variety of causes, some of them quite trivial. The process can be observed in the vessels of the conjunctiva, and electron micrographs demonstrating the difference between healthy erythrocytes and cells from " sludged " blood are reproduced. Apparently there is no deposit of fibrin, at least in the early stages of this type of agglutination, and the effect seems to be reversible. Anoxia is caused not only by slowing of the blood stream, but also by the loss of surface resulting from the agglutination of the erythrocytes.

Basically, "sludging" is probably a protective mechanism, the leucocytes expelled from the clump of erythrocytes lining the vessel walls as a barrier against attack by infecting organisms. Intravascular agglutination is stated to be constantly associated with vascular spasm, and the continued presence of clumps of erythrocytes after relief of the spasm may account for the persistence of anoxic symptoms in the affected organ. Experimentally, "sludging" may be produced by sympathetic stimulation or the injection of adrenaline, and the possibility is discussed that it may also result from conditions of excessive stress, for which the author prefers the term "strain".

F. W. Watkyn-Thomas

1391. **Glomus Jugulare Tumor with Intracranial Extension. Report of a Case Exhibiting Ossifying Obliterative Labyrinthitis**

M. BENNETT, G. M. ZURHEIN, and T. H. BAST. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] 66, 257–265, Sept., 1957. 6 figs., 18 refs.

The association of two apparently unrelated diseases —glomus jugulare tumour and ossifying obliterative labyrinthitis—in the same patient is reported from the University of Wisconsin, Madison. The glomus tumour showed no unusual characteristics apart from its large size. Ossifying labyrinthitis, now an uncommon condition, is usually regarded as secondary to a labyrinthine infection, especially in childhood, epidemic cerebrospinal meningitis being one of its causes. Although cases have been reported of blood being found in the labyrinth in cases of glomus tumour, this disease is not usually recognized as a cause of ossifying labyrinthitis. In the case described there was no previous history of labyrinth trouble, and at necropsy there was no sign of invasion of the labyrinth by the growth, which involved the neck, middle ear, petrous bone, and left middle and posterior cranial fossae. Evidence was found, however, of a previous break, well healed, of the stapedial ligament, and it is suggested that, at one of several operations that had been performed, the stapes was displaced and the labyrinth thus infected. *F. W. Watkyn-Thomas*

1392. **Sudden Deafness and Its Relation to Atherosclerosis**

O. E. HALLBERG. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] 165, 1649–1652, Nov. 30, 1957. 1 fig., 6 refs.

From a study at the Mayo Clinic of 178 cases of sudden deafness of obscure origin the author considers that some 50% of such cases probably have a vascular basis. This is so in patients of all ages; in those in the younger age group, who are not normally regarded as subject to such disease, a proportion give a history of or develop other vascular accidents. In all cases the history should be carefully studied and a full general examination carried out; in doubtful cases the blood cholesterol, fatty acid, and total lipid levels should be determined. The diagnosis is important, because appropriate dietetic and medical treatment may prevent or postpone other vascular accidents. *T. A. Clarke*

1393. **A New Operation to Restore Hearing in Conductive Deafness of Chronic Suppurative Origin**

J. H. T. RAMBO. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] 66, 525–532, Nov., 1957. 16 figs.

The author describes a new operation to eradicate infection and to restore hearing in cases of deafness due to chronic otitis media. An endaural radical mastoidectomy is first performed. Every trace of infected tissue is removed and no attempt is made to preserve the malleus or incus, the retention of an ossicle except the stapes being unnecessary since fenestration of the horizontal canal is always performed, either at the same session or, if necessary, at a later stage, after the plastic operation has healed. When the radical mastoidectomy has been completed and pedicle flaps have been formed from the meatal skin a flap of temporal muscle is turned down into the cavity and over the horizontal canal. This muscle flap has to be raised off the canal when fenestration is performed subsequently and replaced when the second operation has been completed. The skin pedicle flaps are laid over the muscle and packed into place. The author believes that the extra thickness of the covering made by the muscle increases the sound pressure differential between the round window and the fenestra and so aids the hearing. It is noted that earlier attempts to close a total perforation of the drum in cases with a dry middle ear by means of a pedicle flap with fenestration of the canal succeeded initially in 5 out of 10 cases, but in all 5 the new drum was destroyed within 3 to 4 months by cholesteatoma formation from the in-turned epithelial flap. *F. W. Watkyn-Thomas*

1394. **The Rosen Operation—Early Experience**

W. MCKENZIE and E. H. RAINER. *Journal of Laryngology and Otology* [*J. Laryng.*] 71, 655–666, Oct., 1957. 3 figs., 9 refs.

The authors, who worked independently, report one year's experience of Rosen's operation of mobilization of the stapes. Except for minor alterations in the instruments and the use of a meatal incision to widen the field, the technique differed little from that originally described by Rosen. The value of the operation in otosclerosis is discussed. Of 85 patients operated on after otosclerosis had been diagnosed, hearing was improved in 51, unchanged in 31, and worse in only one. In 2 patients whose hearing was found to be worse after mobilization of the stapes improvement was noted following fenestration.

The authors state that in cases of deafness of doubtful nature exploration of the middle ear by Rosen's approach is of value. It was carried out in several cases of conduction deafness, in some of which the middle ear was found to be full of fluid or thick mucus. In one case in which the drums appeared normal an empty oval window was discovered. In 2 other cases hearing improved after division of adhesions.

In the authors' view Rosen's operation is preferable to fenestration, and is suitable in many cases which would otherwise not be considered for surgery.

H. D. Brown Kelly

1395. **Hearing Loss of the Perceptive Type. Incidence and Correlation between Aetiology and Audiometric Pattern**
S. JOHNSEN. *Journal of Laryngology and Otology* [*J. Laryng.*] **71**, 667–672, Oct., 1957. 3 figs., 7 refs.

Among 109,400 children attending normal schools in Copenhagen, the incidence of symmetric perceptive hearing loss proved to be 2 in 1,000. The present study showed a correlation between the aetiology of the hearing loss and the audiometric pattern. Inherited perceptive deafness gives chiefly a graph sloping gradually towards the high frequencies, whereas acquired perceptive deafness gives sharply sloping graphs. Audiograms representing cases in which the aetiology is unelucidated belong in most cases to the gradually sloping type. It is justified, therefore, to conclude that a large proportion of these cases are inherited.—[Author's summary.]

1396. **Two Case Reports of Embryonal Rhabdomyosarcoma with Primary Presentation in the Ear**
C. L. BLANCHARD and H. P. HOUSE. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **66**, 588–591, Nov., 1957. 10 refs.

Embryonal rhabdomyosarcoma is a very unusual condition which, under the name of sarcoma botryoides, was once thought to be limited to the pelvic region. It is now known, however, that it may occur in the head and neck. It is found in children 1 to 6 years old, and it is suggested that it arises in the first branchial arch and Eustachian tube. However, it has also been reported to occur in the orbit and the soft palate. In both the cases here reported the first sign was a soft, painless swelling behind the ear which rapidly enlarged. In one case there was early, widespread lymphatic metastasis, and blood-stained discharge from the ear. In the second there was early facial paralysis and spread occurred into the cranial bones, with metastases in the pelvic and shoulder girdles and the femora. *X*-irradiation resulted in temporary improvement, but both children died. The only hope seems to lie in very early diagnosis. When the ear is affected it is easy to mistake the condition for a low-grade suppuration. The histological diagnosis is not easy, as special stains are needed to show the muscular striae. *F. W. Watkyn-Thomas*

1397. **Individual Differences in Functional Recovery and Structural Repair following Overstimulation of the Guinea Pig Ear**
M. LAWRENCE and P. A. YANTIS. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol. (St Louis)*] **66**, 595–621, Sept., 1957. 12 figs., 13 refs.

At the University of Michigan School of Medicine, Ann Arbor, the individual differences in recovery from acoustic overstimulation were studied in 29 anaesthetized guinea-pigs in which the middle ear had been exposed. Of these animals, 15 were stimulated for 20 minutes by a noise of 150 db. (Group 1) and 14 by a noise of 136 db. (Group 2) at the drum membrane. Each animal was examined by the cochlear-potential method before stimulation, immediately after stimulation, and again after 56 days, when the limit of expected recovery was thought to have been reached. The survivors (10 in Group 1 and 9 in Group 2) were then killed and the cochleae sectioned and examined microscopically.

The amount of loss of hearing immediately after the overstimulation did not seem to influence the rate at which the ear recovered. It is concluded, therefore, that the eventual permanent loss of hearing depends more on the ability of the ear to recover from the overstimulation in the first place than on the amount of overstimulation itself, provided of course that the sensory epithelium is not completely destroyed. If Reissner's membrane is partly damaged it is able to repair itself.
William McKenzie

1398. **Improved Treatment for Allergic Rhinitis**
M. J. MAXWELL. *Lancet* [*Lancet*] **2**, 828–829, Oct. 26, 1957. 1 ref.

A clinical trial of diphenylpyraline, a potent antihistaminic, in 43 patients suffering from chronic allergic rhinitis is reported. The drug was given in capsules, each capsule containing 5 mg. in several hundred tiny pellets which had coatings of varying thickness. The dosage was one capsule night and morning. Of the 43 patients, 34 obtained complete relief of symptoms. The only side-effect was slight drowsiness in 2 patients. [It is implied that symptoms were relieved only while the drug was being taken.] The author states that the blood level of diphenylpyraline is more uniform throughout the 12 hours between doses when the drug is given in these capsules than when it is given in the usual way in the form of a tablet.

[The criteria for the diagnosis of allergic rhinitis in these cases are not stated.]
Norman W. MacKeith

1399. **The Mechanism of Phonation**
V. NEGUS, E. NEIL, and W. F. FLOYD. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol. (St Louis)*] **66**, 817–829, Sept., 1957. 6 figs.

After discussing various theories of the mechanism of phonation the authors describe experiments on cats undertaken at the Middlesex Hospital Medical School, London, to show that phonation does not depend on the clonic contraction of the laryngeal muscles. They showed in fact that there was no clonic muscle response at rates of electrical excitation higher than 250 c.p.s., while above this rate of excitation the muscles went into tonic contraction, as was expected. In a second experiment a slender steel wire was made to rest against the free margin of the thyro-arytenoid fold, its other end being fixed to a diaphragm which conveyed vibrations to a crystal; compression of this crystal produced an electric current which was recorded by means of a piezoelectric transducer. Rhythmical stimulation of the recurrent laryngeal nerve produced vibrations at a frequency of 90 c.p.s., but no vibration at a frequency above 110 c.p.s. was recorded. The results of both experiments, therefore, contradict the theory that phonation is produced by clonic muscle contracture.
William McKenzie

Urogenital System

1400. **Nitrofurantoin in Chronic Urinary Tract Infection**
E. JAWETZ, J. HOPPER, and D. R. SMITH. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 549–557, Oct., 1957. 2 figs., 12 refs.

Nitrofurantoin was administered to patients suffering from chronic urinary tract infection either for short periods (14 to 19 days) or for 4 to 17 months. During nitrofurantoin treatment bacteria could not be cultured from the urine in most cases, but bacteriuria recurred soon after the drug was discontinued. The suppression of bacteriuria was associated with relief from symptoms, and, in some cases with severe renal insufficiency, it resulted in measurable improvement in renal function. Unpleasant side-effects developed in 6 out of 32 patients during the first few days of nitrofurantoin administration. However, the ingestion of maintenance doses (100 to 200 mg. daily) for weeks and months was well tolerated by others.

The protracted administration of nitrofurantoin to patients with ineradicable urinary tract infection, particularly those with chronic pyelonephritis without demonstrable obstruction, may usefully complement the medical management of this difficult problem.—[From the authors' summary.]

1401. **Sulfamethoxypyridazine in Urinary Tract Infections**
A. P. HARRIS, H. D. RILEY, and V. KNIGHT. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 701–708, Nov., 1957. 7 figs., 2 refs.

In this paper from the Vanderbilt University School of Medicine, Nashville, Tennessee, it is reported that after the administration of single doses of 3 g. of sulphamethoxypyridazine (SMP), sulphafurazole (sulphisoxazole; " gantrisin "), and sulphadiazine by mouth to groups of 5 subjects, the average plasma concentration of SMP was almost double that of each of the other sulphonamides, while its concentration in the urine was proportionately less. The clearance of SMP from the blood was relatively slow, and an average plasma concentration of 15 mg. per 100 ml. was maintained with a dose of 1 g. daily. The three drugs were found to be equally active *in vitro* against strains of *Staphylococcus*, *Escherichia coli*, and *Proteus vulgaris*, the most susceptible of the organisms tested, whereas strains of *Aerobacter aerogenes*, paracolon bacillus, and *Pseudomonas aeruginosa* were highly resistant.

In a clinical trial 4 out of 5 patients with severe chronic urinary infection responded to treatment with 1 g. of SMP daily, but only 4 out of the 20 patients receiving 0·5 g. daily exhibited significant improvement. There were no renal or haematological toxic effects, but one patient developed a morbilliform rash which improved promptly when treatment was stopped. *I. Ansell*

1402. **Concepts of Pyelonephritis: Experience with Renal Biopsies and Long-term Clinical Observations**
G. G. JACKSON, K. P. POIRIER, and H. G. GRIEBLE. *Annals of Internal Medicine* [*Ann. intern. Med.*] **47**, 1165–1183, Dec., 1957. 4 figs., 23 refs.

Chronic renal inflammation continues to be an important cause of death and a prevalent clinical problem. This paper from the University of Illinois Hospitals, Chicago, describes the results of kidney biopsy examination in 50 patients with bacteriuria who were classified into three groups: (1) 4 patients with asymptomatic bacteriuria; (2) a broad group of 36 containing (*a*) 7 patients with recurrent acute attacks of pyelonephritis, (*b*) 11 with repeated acute episodes superimposed on chronic symptoms, and (*c*) 18 with chronic symptoms but no acute episodes; (3) 10 patients with azotaemia and/or hypertension, but no or few urinary symptoms. In each case an attempt was made to obtain two biopsy specimens, one for histological examination and the other for culture. There were no deaths in the series, and major complications occurred in only 3 cases, in the form of extrarenal haemorrhage in 2 cases and bacteriaemia with shock in one.

Histologically, 10 specimens were found to be normal. Those from cases of acute infection showed cellular tubular casts and minimal interstitial nephritis. In specimens from patients in the early phases of chronic infection the changes were those of periglomerular inflammation, glomerulitis with intracapsular exudate, and intense interstitial inflammation. In specimens from cases of advanced disease the changes were of two types (1) a thyroid-like architecture, with dilated tubules, atrophic epithelium, and acellular casts, and (2) an infarct-like type, with collapsed tubules and ischaemic and hyalinized glomeruli. In a few patients the final stage showed only scar tissue, with remnants of renal structure and foci of persistent inflammation. Of 12 patients with chronic conditions the primary lesion was complicated by pyelonephritis in 7 (58%). The authors found that severity of the renal lesion increased with the chronicity of the symptoms. Renal function tests, particularly tests of urinary concentration and urea excretion, were the most satisfactory in revealing severe damage, while quantitatively there was decrease in renal plasma flow and glomerular filtration. Of the biopsy specimens from patients with primary pyelonephritis, 56% gave a positive culture, while this figure increased to 80% in those from patients with chronic lesions. Gram-negative bacteria seemed to be more common in acute infections.

The degree of success achieved with antibiotics in treatment decreased markedly with increased duration of symptoms, although recurrences were common even in acute cases. *L. Capper*

Endocrinology

1403. **Polyuria in Hyperparathyroidism**
S. I. COHEN, M. G. FITZGERALD, P. FOURMAN, W. J. GRIFFITHS, and H. E. DE WARDENER. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **26**, 423–431, Oct., 1957. 2 figs., 31 refs.

The authors have investigated the problem of polyuria in 2 patients, a woman aged 53 and a man aged 37, suffering from hyperparathyroidism due to adenoma who were seen respectively at St. Thomas's Hospital, London, and the Royal Infirmary, Cardiff. In spite of fluid restriction and administration of vasopressin the patients continued to pass hypotonic urine, which, however, became more concentrated than the plasma soon after removal of the parathyroid adenoma. This occurred in the presence of a glomerular filtration rate which showed little or no change, suggesting that the polyuria was due not to impaired glomerular filtration, but to tubular dysfunction.

In one of these cases detailed investigation of tubular function was carried out 2 days before and 12 days after parathyroidectomy. Vasopressin and 25% mannitol were given intravenously to increase the output of solute and of antidiuretic hormone. Before operation this procedure rendered the urine (which was already hypotonic) even more dilute and increased the excretion of free water from 0·46 to 2·6 ml. per minute. After operation, although the osmolarity of the urine decreased as a result of the infusion of mannitol, it remained above that of the plasma, and " the calculated excretion of free water ", which was negative, fell from −0·41 to −1·0 ml. per minute. Discussing the change in function which leaves the urine consistently hypotonic the authors suggest that a possible interpretation of their findings is that the tubular dysfunction in hyperparathyroidism is a failure of the second part of the distal tubules and the collecting tubules to concentrate the hypotonic fluid from the first part of the distal tubules. This defect is apparently independent of obvious damage to the kidney substance, as such damage was demonstrated by renal biopsy in one of the authors' cases. *D. G. Adamson*

1404. **Plasma Adrenocorticotrophic Hormone in Addison's Disease and Its Modification by the Administration of Adrenal Steroids**
J. E. BETHUNE, D. H. NELSON, and G. W. THORN. *Journal of Clinical Investigation* [*J. clin. Invest.*] **36**, 1701–1707, Dec., 1957. 4 figs., 27 refs.

There is considerable evidence that there is some reciprocal relationship between adrenal cortical activity and ACTH (corticotrophin) production. There have, however, been no extensive quantitative studies of the plasma levels of ACTH in patients with adrenocortical insufficiency, and in this report from Harvard Medical School, Boston, the authors therefore describe such an investigation. ACTH was assayed by the method of Nelson and Hume (*Endocrinology*, 1955, **57**, 184) in which the concentration of 17-hydroxycorticosteroids in the 10-minute venous effluent from the adrenal gland of a hypophysectomized dog is determined after the intravenous administration of human plasma separated from 40 to 60 ml. of blood. In order to obtain a quantitative result, this response was compared with that following the infusion of standard solutions of pharmaceutical corticotrophin. The method is described in detail, and the results are expressed in milli-units (mU.) per 100 ml. of plasma.

Measured in this way the plasma of healthy subjects and of patients without adrenocortical disease contained no detectable ACTH. The mean plasma level of ACTH in 32 patients with adrenocortical deficiency (29 with Addison's disease and 3 who had undergone bilateral adrenalectomy) was $8{\cdot}4 \pm 7{\cdot}4$ mU. per 100 ml. In 9 cases no ACTH could be detected in the plasma on the first analysis; in 5 of these assay was repeated; 3 were then found to have measurable levels of ACTH activity, but in 2 the results were negative on two and four occasions respectively. The level of plasma ACTH could not be correlated with the duration of the Addison's disease nor with the severity of the pigmentation, but the latter, it is pointed out, may have been modified by previous cortisone therapy.

Infusions of hydrocortisone in doses of 5 to 20 mg. for periods ranging from 2 minutes to 8 hours produced reduction in the plasma ACTH level in all but one of 10 patients with Addison's disease. Neither the rate and concentration of the infusion nor the 17-hydroxycorticosteroid level in the plasma could be directly related to the degree of suppression produced. More limited experiments suggested that prednisone and 9-α-fluorohydrocortisone were potent inhibitors of ACTH secretion, while deoxycortone had little such effect and progesterone had none. *H.-J. B. Galbraith*

1405. **Gonadal Dysgenesis: Modern Concepts**
F. HOFFENBERG and W. P. U. JACKSON. *British Medical Journal* [*Brit. med. J.*] **2**, 1457–1462, Dec. 21, 1957. 4 figs., bibliography.

The authors report their observations on 27 cases of gonadal dysgenesis seen at Groote Schuur Hospital, Capetown, during the past 3 years. Not all the usual criteria of gonadal dysgenesis, namely, sexual infantilism, shortness of stature, associated congenital abnormalities, and high urinary gonadotrophin excretion, were present in all the cases investigated, low gonadotrophin output being observed in several instances; although in the majority of cases this output was high, it was not depressed by cortisone administration. The congenital abnormalities of Turner's syndrome (webbing of the neck, cubitus valgus, naevi, and coarctation of the aorta) were often absent, and frequently there was good breast

development, although in one case an apparently normal breast was shown by biopsy examination to consist only of fat. Pubic and axillary hair was sometimes plentiful, and adrenocortical function, when tested, was found to be normal, even when pubic hair was deficient.

In several patients presenting the appearance of normal females gonadal dysgenesis was proved by laparotomy, which showed the typical "primitive streak". The authors are emphatic that this syndrome is the commonest cause of primary amenorrhoea, irrespective of the physical appearance of the patient. Moreover, some scanty menstrual bleeding has occurred infrequently in such cases. They conclude that female appearance combined with a male nuclear pattern is the most reliable diagnostic criterion—"short of laparotomy". Such patients are female in their orientation and therefore treatment should be directed to further feminization, for which periodic small doses of oestrogen have been found satisfactory. *Nancy Gough*

THYROID GLAND

1406. **The Chronology of Events in the Development of Subacute Thyroiditis, Studied by Radioactive Iodine**
P. Czerniak and A. Harell-Steinberg. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **17**, 1448–1453, Dec., 1957. 1 fig., 12 refs.

It has been demonstrated by a number of authors that in subacute thyroiditis the thyroidal uptake of radioactive iodine (^{131}I) is often low, despite a clinical picture frequently presenting numerous signs of hyperthyroidism, including high levels of serum protein-bound iodine. For this reason, 10 patients have been studied at the Government Hospital, Tel-Hashomer, Israel, over a prolonged period of time, during which they were subjected to tests of the uptake and excretion of ^{131}I every 15 to 30 days during the first 2 months of illness, and then at intervals of 2 to 4 months. The serum level of protein-bound iodine and the erythrocyte sedimentation rate were determined concurrently. From the results obtained, which are tabulated, the authors conclude that the disease develops in 4 functional stages—namely, depression, transition, compensation, and remission—the first lasting for about 2 months, the second being observed during the 3rd month, and the third lasting about another month; in the stage of remission the values for uptake and excretion of ^{131}I and for serum protein-bound iodine gradually return to normal. In all the authors' cases these values all became normal by the 6th or 7th month. *G. B. West*

1407. **A Clinical Study of Chronic Noninfectious Thyroiditis and Autoimmunization**
J. R. Paine, K. Terplan, N. R. Rose, E. Witebsky, and R. W. Egan. *Surgery* [*Surgery*] **42**, 799–813, Nov., 1957. 4 figs., 14 refs.

Serum specimens from a large number of patients with and without thyroiditis were tested for the presence of circulating antibodies to thyroid extract in an investigation described in this paper from the University of Buffalo School of Medicine and the General Hospital, Buffalo, New York. In 120 patients without thyroid disease no antibodies were found, and only 3 out of 29 patients with thyroid disease other than thyroiditis had antibodies in the serum, the specimens in these 3 cases being obtained after operations on the thyroid gland. Antibodies were present in sera from 5 out of 20 patients in whom some type of non-infectious thyroiditis had been diagnosed clinically, and 4 of these patients appeared to be suffering from the subacute or chronic non-specific type of disease. The thyroid gland was examined histologically in 40 cases, and on the basis of the results the cases were divided into 4 groups: (*a*) subacute thyroiditis; (*b*) struma fibrosa (Riedel); (*c*) chronic non-specific thyroiditis; and (*d*) struma lymphomatosa (Hashimoto). Circulating antibodies were found in the sera from some of the patients in the first three groups, but none of the 14 patients with Hashimoto's disease had antibodies in the serum.

In the authors' view, in most cases of thyroiditis circulating antibodies to thyroid extract can be demonstrated in serum during the active phase of the disease, although antibodies will probably be absent when the disease becomes chronic or during a period of remission. They are not present in Hashimoto's disease, and this cannot be called an auto-immune reaction. The authors suggest that an auto-immune process might be considered as a causative agent in other diseases of unknown aetiology. *J. Warwick Buckler*

1408. **Precipitin Tests in Thyroid Disease**
R. B. Goudie, J. R. Anderson, K. G. Gray, D. H. Clark, I. P. C. Murray, and G. P. McNicol. *Lancet* [*Lancet*] **2**, 976–979, Nov. 16, 1957. 2 figs., 13 refs.

The authors, at the Western Infirmary, Glasgow, studied the incidence of precipitating antibodies to human thyroid tissue in specimens of serum from a number of patients suffering from a variety of diseases, sera being examined by a precipitin test in which thyroid extract was used as the antigen. The results were positive in 20 out of 30 patients with Hashimoto's disease, 4 out of 28 with primary myxoedema, and in 3 out of 120 with thyrotoxicosis. Negative results were obtained in 22 patients suffering from other thyroid conditions, including simple goitre and cancer, and in 133 patients who apparently had no thyroid disease. The precipitin test was less sensitive than the serum flocculation test and the serum γ-globulin level. The authors found, as others have done, that with the precipitin test a negative response was sometimes obtained with serum from patients who were undoubtedly suffering from Hashimoto's disease. In their view this is due in some cases to lack of sensitivity, since the complement-fixation reaction was positive in all the untreated and in 15 out of 16 treated cases of Hashimoto's disease. The lack of specificity of the precipitin test is discussed. The authors stress the difficulty of distinguishing some cases of primary myxoedema from cases of Hashimoto's disease. They consider their findings lend support to the view that these two conditions are variants of the same fundamental disease process.

The positive response to the precipitin test of sera from 3 patients with thyrotoxicosis indicated a possible relationship between this condition and Hashimoto's disease. The authors suggest that antigenic material leaks from the thyroid gland and initiates an antibody response which is usually weak and only detectable by the complement-fixation reaction. In a small number of thyrotoxic patients, however, strong antibodies are formed which, by virtue of their cytotoxic properties, produce the thyroid changes of Hashimoto's disease.

D. G. Adamson

1409. **Auto-immunity in Hashimoto's Disease and Its Implications**

D. Doniach and I. M. Roitt. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **17**, 1293–1304, Nov., 1957. 2 figs., 45 refs.

High values for the γ-globulin fraction of the serum protein of patients with Hashimoto's disease have recently been reported. The known association of γ globulins with circulating antibodies and the infiltration of the diseased thyroid gland with plasma cells and lymphoid tissue, which are known to produce antibodies, suggested to the authors that the disease process in this disorder might be explained on the hypothesis that these patients are immunized against an antigen in the thyroid gland. Confirmation of this hypothesis is provided by the results of the present studies, reported from the Middlesex Hospital, London, which demonstrated the presence of thyroid-specific precipitating auto-antibodies in the serum of such patients. The antigen was prepared from thyroid glands obtained at operation or at necropsy on either thyrotoxic or normal subjects, the glands being thinly sliced and allowed to stand " with three parts of 0·9% saline at 2° C. overnight ". For the test this extract, after centrifugation, was diluted threefold with saline. The precipitin tests were carried out on fresh serum. In early experiments the antigen solution was layered directly on to the serum, but diffusion precipitation in agar gels was found to be more sensitive and this was the method used in subsequent experiments.

In 25 out of 30 patients with Hashimoto's disease the serum contained precipitins against saline-extracted human thyroid gland. The thyroid specificity was confirmed by the negative results obtained when the sera were tested against saline extracts of human liver, kidney, spleen, lymph nodes, parotid gland, and brain. Similar precipitin reactions were observed when purified thyroglobulin was substituted for the crude saline extracts of human thyroid. Thyroglobulin was identified as the active antigen, and fractionation of the patients' serum by zone electrophoresis followed by precipitin tests showed that the antibody was located exclusively in the γ-globulin fraction.

Examination of the serum in 5 cases of Hashimoto's disease within one year of partial thyroidectomy showed that in 3 cases the precipitin reaction was still strong, in one it was weak, and in the 5th there was no reaction, although the test was made only 3 weeks after the operation. Of other thyroid diseases, the precipitin tests gave negative results in 105 thyrotoxic patients (whether the disease was active, postoperative, or had been treated) as they also did in 103 patients with non-toxic nodular goitre.

The authors suggest that these findings offer a new approach to the aetiology of lymphadenoid goitre, and continue: " It may be supposed that limited extravasation of thyroglobulin stimulates invasion by lymphoid tissue, with local antibody production. Under certain conditions sufficient antibody may be produced to damage adjacent follicles and release more thyroglobulin. This may in time give rise to a general immune response involving distant parts of the reticulo-endothelial system, with a considerable increase in antibody production, leading to a further lymphoid hypertrophy and progressive damage to the thyroid gland. Classic Hashimoto's disease may represent a late stage in such a sequence of events." They consider that lesser degrees of lymphoid infiltration in other forms of thyroid disease may represent a localized immune response.

John Lister

1410. **The Iodide-repletion Test**

C. D. Burrell and R. Fraser. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **26**, 559–572, Oct., 1957. 4 figs., 33 refs.

The authors describe a standard iodide-repletion test which was evolved at the Postgraduate Medical School of London so that it would be possible to distinguish a state of iodine deficiency from one of mild thyrotoxicosis, and report the results of application of the test in 99 patients. By experiment it was found that 10 mg. of potassium iodide daily for 2 weeks was sufficient to correct the most severe iodine deficiency. In order to prevent suppression of the uptake of radioactive iodine (^{131}I) due to flooding with iodide the test was not performed until 4 weeks after the loading dose.

In 24 out of 25 patients finally diagnosed as having mild thyrotoxicosis the uptake of ^{131}I was high after the loading dose of iodide, while in 29 out of 30 patients suffering from anxiety states who were similarly tested the uptake was normal; 26 of the latter patients had associated non-toxic goitre. All of the 11 patients who had non-toxic goitre, as judged clinically, but who had a high iodine uptake showed a normal or low uptake after the iodide load, while in 7 euthyroid patients the iodine uptake was normal both before and after the iodide-repletion test. Application of the test to 23 patients who had had recent prolonged administration of antithyroid drugs showed that of 6 cases of treated thyrotoxicosis which later relapsed, all showed a high iodine uptake, whereas in 9 out of 10 patients who were found later to be in clinical remission the test gave a normal result. Finally, out of 7 patients suffering from goitrous myxoedema following the administration of either resorcinol or *p*-aminosalicylic acid, 5 showed normal figures after iodide loading, while in the other 2 the figures were near normal.

The authors recommend that the iodide-repletion test should be carried out on all patients showing a high uptake of iodine in the absence of other clinical signs of hyperthyroidism, and also on patients who have been treated with antithyroid drugs. *D. G. Adamson*

1411. **Treatment of Juvenile Thyrotoxicosis with Potassium Perchlorate**
J. M. SMELLIE. *Lancet* [*Lancet*] **2**, 1035–1036, Nov. 23, 1957. 1 fig., 9 refs.

The results obtained with potassium perchlorate in the treatment of juvenile thyrotoxicosis are reported in this paper from the University of Birmingham. The patients, 6 females, were aged 6½ to 13 years at the start of treatment, and the dosage of the drug ranged from 125 to 300 mg. daily. In 2 patients receiving respectively 250 and 300 mg. daily mild hypothyroidism developed, which disappeared when the dose of potassium perchlorate was reduced; there were no other untoward effects. To induce a euthyroid state about 6 weeks' treatment was necessary. In one case treatment was stopped after a period of 9 months and the patient remained well for a further 18 months. In the remaining cases treatment was continued for periods varying from 12 to 36 months; signs and symptoms were controlled but none of the 5 patients had ceased treatment at the time the report was written. *Charles Rolland*

1412. **A Chromatographic Study of Thyroidal Iodine Metabolism in Non-toxic Nodular Goiter**
R. PITT-RIVERS, D. HUBBLE, and W. H. HOATHER. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **17**, 1313–1323, Nov., 1957. 6 figs., 11 refs.

Despite suggestive evidence that the iodide and thyroxine content in non-toxic nodular goitrous thyroid tissue is low, the nature of the biochemical dysfunction is as yet unknown. In this study reported from the National Institute for Medical Research, London, tissue from 15 goitrous patients was examined by ascending chromatography (Harington and Randall's method) after the administration of 200 μc. of radioactive iodine (^{131}I). All but one of the patients (who had premedication with iodide) showed a normal thyroid uptake of ^{131}I, while in all cases the thyroid tissue contained less than normal quantities of thyroxine, both in paranodular and nodular specimens. Separation of the amino-acids moniodotyrosine (MIT) and diiodotyrosine (DIT) revealed a ratio of MIT to DIT which was much higher than normal, even in the paranodular tissue; that is, this ratio showed an inverse relation to the thyroxine content. Examination of the serum from 4 of these cases failed to show the presence of either MIT or DIT, although thyroxine was detected.

Reviewing the accepted steps in the biosynthesis of thyroid hormone, the authors point out that in familial goitrous hypothyroidism one of three defects is thought to exist in addition to an inadequate iodine intake. These are: (1) failure of incorporation of iodide into organic combination; (2) poor conversion of DIT to thyroxine; and (3) a combination of defects, namely, a failure in the synthesis of thyroxine and in de-iodination of MIT and DIT, with the consequent release of these amino-acids into the circulation. The results reported here would suggest that the condition is due to Defect 2 above, so that nodules appear to result from a biochemical insufficiency in the rate of synthesis of required thyroxine. Such a situation is thought likely to occur as the result of a deficiency in the enzymes required to activate DIT.

The findings in this study indicate that iodine deficiency alone does not account for the growth of nodular goitres. *Allene Scott*

1413. **The Value of Globulin-bound Iodine Determination in the Differential Diagnosis of Thyroid Disease.** [In English]
D. WINIKOFF. *Acta endocrinologica* [*Acta endocr.* (*Kbh.*)] **26**, 243–262, Nov., 1957. 6 figs., 31 refs.

At the University of Melbourne, Australia, the distribution of the plasma protein-bound iodine (P.B.I.) between the albumin and globulin fractions has been studied in euthyroid subjects and in 53 hyperthyroid and 16 hypothyroid patients, fractionation of the plasma being performed by the ammonium sulphate precipitation technique of Klein.

A statistically significant difference in regard to globulin-bound iodine (G.B.I.) was demonstrated between the euthyroid and hyperthyroid groups, and determination of the G.B.I. value was found to be the best index for distinguishing between these groups. On the other hand the best index of hypothyroidism was the total plasma P.B.I. value. Treatment with radioactive iodine (^{131}I) or antithyroid drugs resulted in a fall in the levels of both albumin-bound iodine (A.B.I.) and G.B.I. levels, but the decrease in the latter occurred earlier than that in the former; the distribution of bound ^{131}I between the albumin and globulin fractions was similar to that of the stable isotope. Administration of thyrotrophic hormone to 5 cases of Sheehan's disease resulted in an increase in the P.B.I. value, this being reflected in both the A.B.I. and the G.B.I. values. Thus determination on several occasions of the G.B.I. level in the conditions described is considered to be of value in the differential diagnosis of thyroid disease. It is concluded that thyroxine is in a state of dynamic equilibrium in its distribution between the plasma proteins, the actual distribution found being affected by the methods employed for separation of the fractions.
F. W. Chattaway

1414. **Clinical Progress in the Treatment of Exophthalmos of Graves' Disease, with Particular Reference to the Effect of Pituitary Surgery**
E. P. MCCULLAGH, M. CLAMEN, and W. J. GARDNER. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **17**, 1277–1292, Nov., 1957. 10 figs., 19 refs.

The exophthalmos of Graves's disease is believed to be due to hypersecretion of thyroid stimulating hormone or of a closely related material which has been called "exophthalmos-producing substance". It has been shown that after control of the hyperthyroidism the exophthalmos subsides in nearly 60% of cases, fails to improve in about 40%, and becomes extremely severe in about 1%. Attempts at reducing exophthalmos, apart from orbital decompression, have largely been directed at suppression of pituitary hyperactivity. The present

authors report, from the Cleveland Clinic, Ohio, their experience in the use of *x*-ray therapy, thyroid hormones, and ACTH or cortisone for this purpose, and describe in more detail the results in 9 cases treated by surgery of the hypophysis.

X-ray treatment to the pituitary region in doses of 2,000 to 4,000 r. at the surface was found to be of doubtful value. Improvement in the exophthalmos has been reported sometimes to follow the use of desiccated thyroid or thyroxine, and the authors have observed 20 patients with progressive exophthalmos who were treated with triiodothyronine over periods varying from 2 to 11 months. Proptosis was reduced by 2 mm. or more in 9 of these cases, remained stationary in a further 9, and increased in 2. In 10 patients treated with ACTH (corticotrophin) in a dose of 40 mg. given intravenously 6-hourly for 5 to 16 days, with or without hydrocortisone in addition in an initial dose of 200 mg. orally daily with gradual diminution of the dosage, over many weeks there was clinical improvement in all cases. The 9 patients subjected to hypophyseal surgery were treated either by section of the pituitary stalk or cauterization of the anterior lobe of the gland, or both. These procedures were performed only in cases in which non-surgical methods had failed and the condition was extremely severe. In all 9 patients the exophthalmos improved postoperatively, in some almost disappearing, and visual acuity that had been extremely poor returned to normal. The authors note that after cauterization of the anterior pituitary lobe and severing of the stalk the subsequent hypopituitarism develops more rapidly and is more severe than that which follows section of the stalk alone. Of the 9 patients treated surgically, 2 died during the postoperative period, one as the result of an operation accident and the other from massive pulmonary emboli. In the remaining 7 cases the resulting hypopituitarism was controlled by a combination of thyroid hormones, steroids, and stilboestrol.

The authors admit that additional observations are needed and remark that it will be particularly interesting to learn what degree of hypopituitarism and improvement in ocular signs will consistently follow section of the pituitary stalk, which is a relatively non-traumatic procedure compared with cauterization of the pituitary or hypophysectomy. *John Lister*

1415. **Adrenocortical Function in Myxedema**

G. A. WILLIAMS, K. R. CRISPELL, and W. PARSON. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **17**, 1347–1353, Nov., 1957. 2 figs., 23 refs.

In order to clarify the conflicting reports which have appeared in the literature with regard to the concept that adrenocortical function is depressed in myxoedema a study was undertaken at the University of Virginia School of Medicine, Charlottesville, of 13 patients with myxoedema (10 idiopathic cases, 2 post-thyroidectomy, and one post-irradiation). The basal metabolic rate ranged from −28 to −44%, the serum cholesterol level was high in all cases, and in most of the cases the uptake of iodine was below 12%. Three tests were performed: (1) determination of the plasma levels of free 17-hydroxycorticosteroids before and after stimulation with 25 units of ACTH intravenously (these values gave a measure of the adrenal cortical responsiveness and reserve respectively); (2) 17-ketosteroid excretion in 24 hours (9 patients); and (3) in 3 cases the biological " half-life " of intravenously administered hydrocortisone was determined by means of serial estimations and compared with that in 3 normal subjects.

In all cases the pre-ACTH level of 17-hydroxycorticosteroids in the plasma was normal, while the post-ACTH levels showed the normal (triple) increase in all but 2. In all but one the urinary 17-ketosteroid excretion was below normal, while the half-life of hydrocortisone proved to be much longer in the myxoedematous patients (3 hours compared with 2·3 hours in controls). Once the thyroid deficiency was corrected the abnormal values returned to normal. These results suggest that adrenal function and functional reserve are essentially normal, but that there is a diminished rate of metabolism of adrenal corticosteroids in myxoedema. *Allene Scott*

DIABETES MELLITUS

1416. **Hydrocortisone in Necrobiosis Lipoidica Diabeticorum**

R. H. MARTEN and M. DULAKE. *British Journal of Dermatology* [*Brit. J. Derm.*] **69**, 395–399, Nov., 1957. 6 refs.

At King's College Hospital, London, local injections of hydrocortisone acetate in normal saline were tried in the treatment of necrobiosis lipoidica diabeticorum in 4 patients (2 male and 2 female) who had had diabetes for 6 to 18 years and necrobiosis without remission for 2 to 5 years. The injections were given at weekly intervals directly into the lesions, which were mainly on the legs, in a strength of 25 mg. per ml. (14 lesions) and 50 mg. per ml. (4 lesions), the volume injected varying from 0·05 to 2 ml. Biopsy specimens were taken before, during, and after completion of the treatment. In 17 of the 18 lesions there was marked improvement or complete resolution and in one slight improvement. In one patient, however, 5 lesions relapsed 24 to 46 weeks after cessation of treatment. Complications included ulceration on 3 occasions, 2 of the ulcers developing after injection of the stronger solution, and cellulitis in 2 cases. The authors state that the number of injections necessary to bring about maximum improvement varied from 4 to 12, the majority of the lesions receiving 4 or 5. *E. W. Prosser Thomas*

1417. **24-hour Urinary Pepsinogen Excretion in Juvenile Diabetes**

H. G. GRAYZEL, H. B. WARSHALL, B. ELKAN, and A. STERNBERG. *Diabetes* [*Diabetes*] **6**, 480–484, Nov.–Dec., 1957. 33 refs.

It has been claimed that the uropepsin content of the 24-hour specimen of urine may provide an indirect measure of pituitary–adrenocortical activity. Since disturbances of pituitary–adrenal function are thought to

play an important part in the diabetic state the authors undertook a study of urinary uropepsin excretion in 74 cases of juvenile diabetes at the Jewish Hospital of Brooklyn, New York. A control group of 26 healthy children and adults was also studied.

The mean uropepsin excretion in 24 hours for normal subjects was 1,872 (±549) units, and for all the diabetics 3,000 (±920) units. For diabetics with over 10 years' history of the disease the value was 4,133 (±1,680) units, uropepsin excretion rising progressively with the duration of the diabetes. The significance of these findings in relation to pituitary and adrenal function is briefly discussed. *C. L. Cope*

1418. **Aspirin and Diabetes Mellitus**
J. Reid, A. I. Macdougall, and M. M. Andrews. *British Medical Journal* [*Brit. med. J.*] **2**, 1071–1074, Nov. 9, 1957. 2 figs., 15 refs.

A study is reported from Western Infirmary, Glasgow, of the effect of aspirin in diabetes mellitus. A dose of 1 to 1·6 g. of the drug was given every 4 hours (one dose being omitted at night) for 14 days to 8 patients, aged 15 to 65 years, who had had diabetes for an average of 2 years. The mean fasting blood sugar level (7 patients) fell from 197 mg. per 100 ml. to 92 mg. per 100 ml. and the mean urinary excretion of sugar (6 patients) fell from 38 g. per 24 hours to less than 5 g. per 24 hours. The blood sugar curves after a dose of 50 g. of glucose by mouth (5 patients) were uniformly lower during salicylate administration, while the basal metabolic rate increased. In 2 patients with moderate ketonuria before treatment the urinary excretion of ketones fell to normal at the end of the second week of treatment. No significant changes in body weight were observed. Persistent nausea developed in 2 patients given large doses of aspirin to build up the blood salicylate level (50 mg. per 100 ml. serum), while 2 patients complained of tinnitus and 7 of dullness of hearing. All these toxic manifestations disappeared soon after aspirin administration was discontinued. *W. J. H. Butterfield*

1419. **Certain Aspects of the Mode of Action of Hypoglycaemia-producing Sulphonamides Demonstrated in Normal and Diabetic Subjects by Their Effect on Intravenous Loading with Fructose.** (Aspects du mode d'action de certaines substances sulfamidées hypoglycémiantes révélés chez l'homme normal et diabétique par leur effet sur des surcharges intraveineuses de fructose) D. Bonhôte. *Schweizerische medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **87**, 1318–1321, Oct. 26, 1957. 4 figs., 29 refs.

In a study of the mode of action of the hypoglycaemic sulphonamides, carried out at the University of Zürich, 0·5 g. of fructose per kg. body weight was infused in 300 ml. of water intravenously over a period of 30 minutes in 6 non-diabetic subjects and 3 diabetic patients and the capillary blood glucose level estimated before and at intervals of 30, 60, 90, and 180 minutes after the infusion by the glucose oxidase method of Froesch and Renold (*Diabetes*, 1956, **5**, 1), which is specific for glucose and is not affected by fructose.

The test showed that the infusion was followed by a slight transient rise in blood glucose level in the non-diabetic subjects. Paradoxically this effect was enhanced to a slight degree by previous administration of a hypoglycaemic sulphonylurea compound. In the diabetic subjects, however, the hyperglycaemic effect of the infusion was more marked, while the initial blood glucose level was reduced by previous administration of the hypoglycaemic sulphonylurea and the hyperglycaemic curve was likewise flattened. The rapid infusion of the same quantity of fructose over 10 to 12 minutes in a normal man was accompanied by a fall in the blood glucose level of about 25 mg. per 100 ml. In the same subject after administration of the sulphonylurea compound a similar infusion was accompanied by a paradoxical rise in the blood glucose level of about 13 mg. per 100 ml.

The response in the diabetic subjects was in keeping with the suggested action of the sulphonylureas, that is, of inhibiting hepatic glycogenolysis (in addition to their main action of stimulating the secretion of insulin). The paradoxical effect in non-diabetic subjects could not be explained. *Robert de Mowbray*

1420. **The Potentiation of Exogenous Insulin by Tolbutamide in Depancreatized Dogs**
R. Caren and L. Corbo. *Journal of Clinical Investigation* [*J. clin. Invest.*] **36**, 1546–1550, Nov., 1957. 17 refs.

In experiments carried out at the University of California School of Medicine, Los Angeles, on depancreatized dogs, insulin and tolbutamide were administered separately and together by the intravenous route and the effect on the blood sugar level studied. The results suggested that tolbutamide potentiates the action of exogenous insulin in the absence of all pancreatic tissue, augmenting both its intensity and its duration. Tolbutamide alone did not reduce the blood sugar level in any animal. *A. I. Suchett-Kaye*

1421. **Further Characterization of an Insulin Antagonist in the Serum of Patients in Diabetic Acidosis**
J. B. Field, F. Tietze, and D. Stetten. *Journal of Clinical Investigation* [*J. clin. Invest.*] **36**, 1588–1593, Nov., 1957. 1 fig., 13 refs.

The authors, working at the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, have previously reported (*Diabetes*, 1956, **5**, 391; *Abstr. Wld Med.*, 1957, **21**, 338) the occurrence of an insulin antagonist in the serum of patients in diabetic acidosis which is of protein nature, is inactivated at 100° C., and does not exhibit any insulinase activity. In the present paper they report the following further characteristics of this substance. It is not inactivated by trypsin, but is destroyed by chymotrypsin. On electrophoresis it migrates with the α_1-globulin fraction of the serum proteins. It has no glucagon-like activity, and is capable of inhibiting the ability of human insulin, as well as of beef and pork insulin, to augment glycogen deposition by the rat hemidiaphragm *in vitro*.

[The aetiological significance of this insulin antagonist in human diabetes has yet to be demonstrated.]
A. I. Suchett-Kaye

The Rheumatic Diseases

1422. **Objective Evaluation of Patients with Rheumatic Diseases. III. Comparison of Serum Glycoprotein, Seromucoid, and C-reactive Protein Determinations as Methods for the Evaluation of Patients with Rheumatic Fever**
M. R. SHETLAR, R. W. PAYNE, H. B. STRENGE, and J. B. FAULKNER. *Journal of Pediatrics* [*J. Pediat.*] **51**, 510–515, Nov., 1957. 3 figs., 12 refs.

A comparative study of the value of various laboratory procedures in the estimation of the severity and duration of disease activity in rheumatic fever was undertaken at the Veterans Administration Hospital and Oklahoma School of Medicine, Oklahoma City. The authors determined the serum concentrations of glycoprotein, seromucoid (using tryptophan estimation), and C-reactive protein, and the serum antistreptolysin-O titre, comparing the values obtained with the erythrocyte sedimentation rate (E.S.R.) [method not stated] and the clinical findings. There was some overlapping between patients with "active" and those with "inactive" disease with all these tests, but each one (with the exception of the antistreptolysin-O titre) appeared to be measuring a similar type of change, although the changes took place at different rates.

The most rapid response to changes in disease activity was obtained with the C-reactive protein test, the results of which became negative very quickly after clinical disease activity had subsided. The E.S.R. returned to normal more slowly than did the other values; it was raised in 13 out of 18 cases of inactive and in 14 out of 16 cases of active disease. The serum glycoprotein level, whether estimated as mg. of bound hexose per 100 ml. of serum or as a percentage of the total serum proteins, was raised in all 18 cases of active disease, as was the seromucoid level. The former was raised in 9 out of the 21 inactive cases and the latter in 4 out of 16 such cases. The antistreptolysin-O titre showed no clear relationship with inflammatory activity.

E. G. L. Bywaters

1423. **Ankylosing Spondylitis and Chronic Inflammatory Lesions of the Intestines**
V. L. STEINBERG and G. STOREY. *British Medical Journal* [*Brit. med. J.*] **2**, 1157–1159, Nov. 16, 1957. 20 refs.

In this paper from the London Hospital the authors present the clinical details of 6 patients, 5 men and one woman aged from 42 to 50, in whom chronic inflammatory lesions of the intestines were associated with clinical and radiological evidence of ankylosing spondylitis (although in 2 cases only the sacro-iliac joints and the symphysis pubis were involved). In 4 of the 6 cases the clinical, radiological, and sigmoidoscopic picture was that of chronic ulcerative colitis, and in these 4 cases this disease had been present for some years before the onset of back pain. The one female patient had histologically proved Crohn's disease and was found, radiologically, to have ankylosing spondylitis involving the sacro-iliac joints and pubic symphysis; she developed chronic ulcerative colitis 2 years later. The 6th patient also had Crohn's disease and in this case the radiological appearances of ankylosing spondylitis developed in both sacro-iliac joints 9 years later.

The authors consider that the association between ulcerative colitis and ankylosing spondylitis is not fortuitous and suggest that ankylosing spondylitis represents a non-specific reaction to disease of the intestines.

J. Warwick Buckler

1424. **Serological Reactions to Polysaccharides in Rheumatoid Arthritis**
J. P. GOFTON, J. W. THOMAS, and H. S. ROBINSON. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **77**, 1098–1102, Dec. 15, 1957. 12 refs.

The original methods for the demonstration of a "rheumatoid factor" in the serum of patients with rheumatoid arthritis by means of an agglutination reaction were those set out by Rose and Waaler, using sensitized sheep erythrocytes. Singer and Plotz have since shown that the sheep cells can be replaced by polystyrene globules or latex particles, and Heller that the sensitizing serum can be replaced by Cohn's Fraction II of human serum. [Rheins *et al.* have shown that γ globulin from the serum of numerous animal species will react with the "rheumatoid factor" and give equivalent results.]

In the present paper from the British Columbia Medical Research Institute, Vancouver, it is stated that the "rheumatoid factor" will react in a similar way with latex particles treated with chondroitin sulphate, hyaluronic acid, or heparin. Sera from 312 patients, including 71 with rheumatoid arthritis, were examined, the standard latex fixation test being performed simultaneously with latex particles treated with Fraction II, with untreated latex particles, and with latex particles treated with each of the three polysaccharide substances. The results obtained with each method are discussed at some length and it is concluded that the specificity of the tests with the polysaccharides is comparable to that of the standard latex fixation test, though the possibility is admitted "that small quantities of active globulin are present as a contaminant in the various polysaccharide preparations". One important implication of these findings is the possibility that an auto-immune reaction between these polysaccharide components of joint tissues and the "rheumatoid factor" in the serum may supply the basis of the chronic inflammatory process of rheumatoid arthritis.

Harry Coke

1425. **Concentration of Penicillin in the Serum following Intramuscular Administration of Benzathine Penicillin G to Children with Inactive Rheumatic Fever**
R. I. LADE, A. M. DIEHL, I. SNYDER, and T. R. HAMILTON. *Pediatrics* [*Pediatrics*] **21**, 233–242, Feb., 1958. 6 figs., 17 refs.

COLLAGEN DISEASES

1426. **Renal Involvement in Progressive Systemic Sclerosis (Generalized Scleroderma)**
G. P. RODNAN, G. E. SCHREINER, and R. L. BLACK. *American Journal of Medicine* [*Amer. J. Med.*] **23**, 445–462, Sept., 1957. 8 figs., 44 refs.

The authors report, from the University of Pittsburgh School of Medicine, the detailed clinico-pathological investigation of 9 patients with systemic scleroderma, of whom 7 died as a result of malignant hypertension and rapid renal failure; of the other 2 patients, one had only mild renal dysfunction and in the other extensive renal lesions were discovered only post mortem. In the 7 fatal cases the termination of the illness was characterized by the development of headaches, failing vision, and hypertension. In some cases uraemic coma and convulsions supervened immediately before death, which occurred within a few months of the clinical recognition of renal involvement. Only 3 of the patients had not received steroid therapy during the course of their illness. Histological examination of the kidneys in 6 cases revealed three striking pathological changes, consisting in (1) intimal thickening of small interlobular arteries and arterioles, (2) fibrinoid necrosis of afferent arterioles and glomerular loops, and (3) multiple cortical infarcts; similar changes were found in the viscera.

Reviewing the literature the authors note that renal involvement in systemic sclerosis is by no means rare, although often there may be no clinical manifestations. The precise role of ACTH and cortisone in the development of these renal lesions is discussed, but neither the literature on the subject nor the authors' investigations provide a satisfactory explanation. There is, however, some evidence that the use of hypotensive drugs may initiate renal failure in patients whose hypertension is related to systemic sclerosis. On the other hand it has been held that the renal changes may result from the hypertension itself—whatever its cause in systemic sclerosis—but the authors describe one case in a patient with typical renal changes who remained normotensive throughout the disease. They conclude that renal involvement in systemic sclerosis occurs more frequently than has been supposed, that this represents true involvement of the kidney in this disease, and that the ensuing malignant hypertension, although it adds its particular signature to the renal pathology, does not account for all the changes that may be demonstrated.

J. N. Harris-Jones

1427. **Familial Hypergammaglobulinaemia and Systemic Lupus Erythematosus**
T. LEONHARDT. *Lancet* [*Lancet*] **2**, 1200–1203, Dec. 14, 1957. 2 figs., 41 refs.

It is well recognized that there is an association between systemic lupus erythematosus (S.L.E.) and hypergammaglobulinaemia. There is evidence of an inherited tendency in both discoid lupus erythematosus and agammaglobulinaemia. The author of this paper from Malmö General Hospital, Sweden, attempts to demonstrate an inherited tendency for the association of S.L.E. with hypergammaglobulinaemia. He describes 4 siblings (sisters) out of a family of 14 in which hypergammaglobulinaemia was "strikingly frequent".

In 2 of the 4 siblings the diagnosis of S.L.E. was established beyond doubt, and both of these died from the disease; in one of them severe relapses occurred following administration of phenylbutazone. S.L.E. was also diagnosed in a third sister (a twin), although the presence of L.E. cells was not demonstrated. The fourth sister, who had received treatment for gonorrhoea, complained of arthralgia; in this patient the erythrocyte sedimentation rate was raised and the results of flocculation tests were abnormal. All 4 sisters had hypergammaglobulinaemia. Of the 14 siblings, 6 were considered to show a moderate increase in the gamma-globulin fraction—0·94 to 1·17 g. per 100 ml.; in 4 others it ranged from 1·37 to 1·46 g. per 100 ml.; and in one a level of 3·78 g. per 100 ml. was recorded.

In this sibship, therefore, the author found 3 cases of S.L.E. and a significantly high incidence of hypergammaglobulinaemia in the remainder. It is suggested that the inherited mechanism is a tendency towards overproduction of antibodies and gamma globulin. Once hypergammaglobulinaemia is established unfavourable antigens may provoke S.L.E. In support of this theory the author cites the sibling who, known to have marked hypergammaglobulinaemia, developed classic S.L.E. following treatment with phenylbutazone.

J. N. Harris-Jones

1428. **Incidence of Disseminated Lupus Erythematosus. Follow-up Studies Indicating Increased Frequency**
A. SVANBORG and L. SÖLVELL. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **165**, 1126–1128, Nov. 2, 1957. 9 refs.

The authors attempt to show that there has been a real increase in the incidence of disseminated lupus erythematosus and not an apparent one as the result of improved methods of diagnosis. All patients with symptoms conceivably due to systemic lupus erythematosus admitted to the two main clinics at Sahlgren's Hospital, Gothenburg, Sweden, during 1938 and 1939, 1948 and 1949, and 1954 and 1955 were followed up. The diagnosis was based on the clinical features and not only on a positive reaction to the L.E.-cell test. The diagnostic criteria, therefore, were considered to be the same throughout the 6-year period. Patients in whom the clinical features might represent the early phase of systemic lupus erythematosus were recalled for review; if death had intervened necropsy records, when available, and death certificates were scrutinized.

It was found that whereas systemic lupus erythematosus was diagnosed in one case in 1938, it was diagnosed in 9 in 1955. After allowing for an increase in the population of the city and in hospital attendances during this period, the authors were satisfied that this increase was statistically significant. They attempt to relate this increase to the growing use of chemical compounds in both medical treatment and also in foodstuffs.

[Neither the methods adopted nor the results seem entirely convincing. In systemic lupus erythematosus, more perhaps than in any other disease, the clinical diag-

nosis requires confirmation, and it is therefore doubtful whether any series of cases seen before the introduction of the L.E.-cell test is truly comparable with a series seen after the introduction of that test.]

J. N. Harris-Jones

GOUTY ARTHRITIS

1429. **Treatment of Acute Gouty Arthritis with Demecolcine**

J. COLSKY, S. WALLACE, and M. M. BANOWITCH. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **100**, 765–773, Nov., 1957. 5 figs., 14 refs.

Demecolcine, which is closely related chemically to colchicine, was given to 26 patients at Maimonides Hospital, Brooklyn, New York, for a single attack of acute gouty arthritis. In one patient there was associated polycythaemia vera. The drug was given by mouth in a total dosage of 8 to 10 mg. to 20 patients, 5 to 6 mg. to 5, and 2 mg. to one. In some instances 1 mg. was administered at hourly intervals with or without an initial loading dose, and in others the total amount was given in a single dose. The response was equally rapid with either method of administration. Complete remission was obtained in 18 cases and a partial response in 3; 5 patients showed no improvement at all, 3 of these being given colchicine subsequently, also without effect. Improvement usually began 4 to 6 hours after the start of treatment and was maximal 12 to 18 hours later, although in some cases objective improvement was delayed 24 to 36 hours. No change was observed in the serum uric acid level, which ranged from 6 to 12 mg. per 100 ml., but the leucocyte count, which initially was within the normal range, tended to fall slightly. Side-effects included mild nausea in 2 patients, mild diarrhoea in 2, and temporary alopecia in 2, one of whom developed a maculopapular pruritic rash. Panhaemocytopenia occurred in 2 cases in which daily maintenance doses of 1 to 3 mg. had been given together with several courses each of 8 mg.; the blood picture returned to normal 2 to 3 weeks after withdrawal of the drug.

The authors conclude that although the gastro-intestinal side-effects of demecolcine are much less severe than those of colchicine, the latter is the drug of choice in the treatment of gouty arthritis in view of the potent bone-marrow-depressing effects of demecolcine.

M. Kendal

1430. **Vascular Changes in the Acute Attack of Gout and the Favourable Effect of Their Modification.** (Alteraciones vasculares en el ataque agudo de gota e influencia favorable de su modificacion)

C. JÜNEMANN B., R. DOMINGUEZ A., R. BERRIOS DE LA L., O. MELENDEZ E., E. ACEVEDO, and P. CASTILLO. *Revista médica de Chile* [*Rev. méd. Chile*] **85**, 355–371, July, 1957 [received Jan., 1958]. 3 figs., 33 refs.

The authors, writing from the University of Chile, Santiago, review the anatomy and physiology of capillary arterio-venous shunts in the peripheral circulation in man, as described by Chambers and Zweifach, Vogler, and others, and discuss the theory of Wood (*Brit. med. J.*, 1950, **1**, 562) that these small anastomoses are implicated in the production of the pain, heat, and redness of the para-articular skin in acute gout. In the normal leg the amplitude of pulsation recorded by an oscillometer decreases with the distance from the trunk. In the leg affected by acute gout, however, the authors have confirmed the finding of Wolfson and Robinson (*J. Lab. clin. Med.*, 1951, **38**, 951) that pulsation in the inferior tibial region is greater than that in the femoral region.

" Hydergine " (a preparation of ergot alkaloids) in a dose of 2 ml. was injected into the femoral or brachial artery of the affected limb in 4 cases of acute gouty arthritis, smaller doses being subsequently given, first by intramuscular injection and then by mouth, for periods up to 15 days. In a further 4 cases the initial intra-arterial injection was omitted but the treatment was otherwise the same. An improvement was observed in the affected joint within 5 minutes of the intra-arterial injection of hydergine, the skin becoming pale and the part less painful, while the abnormal oscillometer gradient was reversed. The peri-arterial injection of procaine did not produce the same effect. In the second group of cases the action of hydergine was less spectacular, but the treatment was considered to produce a similar degree of improvement [there were no controls] in about 2 days, after which it was continued for maintenance purposes. In neither group were the symptoms completely abolished by hydergine therapy.

Allan St. J. Dixon

1431. **Intravenous Colchicine in the Treatment of Acute Gout.** (Colchicina intravenosa en el tratamiento de la gota aguda)

M. LOSADA L., A. LOSADA L., and O. FRANCE S. *Revista médica de Chile* [*Rev. méd. Chile*] **85**, 372–374, July, 1957 [received Jan., 1958]. 1 fig., 12 refs.

The authors briefly review the pharmacology and therapeutic use of colchicine, with particular reference to the recent introduction of preparations suitable for intravenous injection, and report the results obtained at the Hospital del Salvador, Santiago de Chile, in the treatment of acute gout in 18 men and 2 women with demecolcine (deacetylmethylcolchicine) given intravenously in doses up to 3 mg. daily. A total dose of 9 mg. or less was sufficient in 16 of the 20 cases to abort the attack. Improvement, which was spectacular in 9 cases, was obtained in all of them, usually beginning within 24 hours of starting treatment. Complete remission occurred within 72 hours in 12 cases, but in others took as long as 12 days. There were 2 cases of periphlebitis at the site of injection, one of which was severe, and tenderness of the vein without signs of inflammation occurred in a third case. Diarrhoea developed in 5 cases, nausea and vomiting in 4, and intestinal colic in one; 6 of these patients had shown similar intolerance of oral colchicine preparations. In most of the cases, however, intravenous colchicine therapy was effective and well tolerated. *Allan St. J. Dixon*

[This paper was also published in *Revista Clínica Española*, 1957, **67**, 170.—EDITOR.]

Neurology and Neurosurgery

1432. **The Electroencephalogram and Mental Activity**
A. C. MUNDY-CASTLE. *Electroencephalography and Clinical Neurophysiology* [*Electroenceph. clin. Neurophysiol.*] **9**, 643–655, Nov., 1957. 8 figs., 34 refs.

The author, working at the National Institute for Personal Research, Johannesburg, has studied the electroencephalograms (EEGs) of 72 normal adult Europeans and of 66 normal adult Africans. Automatic frequency analysis was utilized in all recordings, and eye-opening and eye-closure were carried out repeatedly. During the recordings 64 of the Europeans and 59 of the Africans were given simple arithmetical problems to solve, and 59 of the Europeans were also given instructions involving visual, auditory, or kinaesthetic image-formation, changes associated with these activities being noted. Another 304 routine records taken from hospital patients without organic cerebral disease were divided into two broad groups, one containing all those (137) from patients whose case histories included some comment on bad temper, emotional disturbance, or emotional instability with behaviour disorder and the other those (167) from individuals who were apparently mentally stable; the two groups of records were then compared in respect of the occurrence and nature of theta (4- to 7-c.p.s.) activity.

No important differences were found between the records of Africans and Europeans. It was confirmed that blocking of alpha activity is far greater with visual than with mental processes, and with visual imagery and mental arithmetic than with auditory or kinaesthetic imagery. Alpha rhythm can also be fully blocked without conscious involvement of visual activities by an attention or alerting factor. However, it was shown that concentrated attention, as during mental arithmetic, or visual imagery, can occur without blocking of the alpha rhythm, so that the relationship is not invariable. Rhythms of alpha frequency from the frontal and anterior temporal areas can be classed as "alphoid" and are unaffected by attention. The author's findings suggest that theta activity may be of at least four separate types, one of which is an alpha variant, while another, though not harmonically related to the alpha rhythm, is suppressed by attention. A third type of theta activity is augmented by perceptual activity but not by affective change, while a fourth appears to vary with emotional activity. Similarly, two types of fast or beta activity were found, one of which seemed to be a fast alpha variant, suppressed during cortical activity, while the other was augmented by attention. *John N. Walton*

1433. **Effect of Artificial Ionization of the Air on the Electroencephalogram. Preliminary Report**
D. SILVERMAN and I. H. KORNBLUEH. *American Journal of Physical Medicine* [*Amer. J. phys. Med.*] **36**, 352–358, Dec., 1957. 3 figs., 20 refs.

1434. **A Study of 137 Cases of Anencephaly**
V. P. COFFEY and W. J. E. JESSOP. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **11**, 174–180, Oct., 1957. 15 refs.

This study is based on 137 cases of anencephaly occurring among 23,085 births at three maternity hospitals in Dublin. The incidence, 5·9 per 1,000 births (8·6 per 1,000 in one of the hospitals), is higher than that reported from any other area. In all but one case the sex was recorded, there being 26 males to 110 females, a ratio of 1:4·2, but of the 13 foetuses which had reached a maturity of 40 or more weeks, 5 were male. The mothers of the 137 anencephalic infants were compared with 192 mothers of normal babies born at the same hospitals. The age of distribution of the mothers of the anencephalics was significantly higher than that of the controls, but parity had no apparent effect when correction was made for maternal age. A significantly higher proportion of the mothers of anencephalics (67·8%) than of the controls (55%) were of Blood Group O. The mothers of anencephalics did not differ from the controls in nutritional status, but a significantly higher proportion of them (35·5 to 24·5%) had a haemoglobin level below 70% and a plasma protein level below 5·5 g. per 100 ml. Also more mothers of anencephalics had suffered an illness in the first trimester of pregnancy than had the control mothers. Of the 98 multiparae among the mothers of anencephalic children, 6 had had one previous anencephalic baby and one 2 such babies. It is stated that "there would seem to be a definite association between anencephaly and defective nutrition" of the mother, but not all workers have confirmed this. *C. O. Carter*

1435. **Ophthalmological Basis for a Classification of Amaurotic Idiocy.** (Bases ophtalmologiques d'une classification des idioties amaurotiques)
P. DANIS, C. BÉGAUX, and G. DECOCK. *Journal de génétique humaine* [*J. Génét. hum.*] **6**, 91–155, Sept., 1957. 17 figs., bibliography.

This paper from the Institut Bunge, Antwerp, supplements a previous study by van Bogaert and Klein (*J. Génét. hum.*, 1955, **4**, 23) of the ophthalmological aspects of amaurotic idiocy. From an ophthalmoscopic and histological study of the eyes in one infantile and 2 juvenile cases and an exhaustive analysis of the literature the authors conclude that there are two distinct types of the affection—one in which there is degeneration of the ganglion cells of the retina, giving the classic cherry-red spot, and another in which disintegration of the neuroepithelium with a concomitant reaction of the pigment epithelium gives rise to the classic juvenile fundus lesion.

The authors suggest that four types of case may be distinguished clinically: (1) with the cherry-red spot at the macula; (2) with pigmentary changes of the fundus;

(3) with isolated optic atrophy; and (4) with a normal fundus. Within any particular family only one type is seen, though the age of onset may vary. With such a classification the difficulty of accounting for the various intermediate types, such as the late infantile and adult forms, disappears. It is certainly true that amaurotic idiocy with normal fundi is more likely to be seen in the adult than in the child. *Arnold Sorsby*

1436. **Supratentorial Tumours in Childhood.** (Les tumeurs supratentorielles de l'enfant)
J. E. PAILLAS, R. VIGOUROUX, G. PIGANIOL, and R. SEDAN. *Neuro-chirurgie* [*Neuro-chirurgie*] **3**, 165–179, July–Sept. [received Dec.], 1957. 3 figs.

Among 92 pathologically proven cerebral tumours in children under the age of 15 seen at the Hôpital de la Timone, Marseilles, 44 were supratentorial, 20 being situated in the midline and 24 laterally placed. In more than half the cases the first sign was evidence of increased intracranial pressure, and the first symptom was headache or more rarely vomiting. Early papilloedema was seen in 11 patients and optic atrophy in 3. The illness began with motor weakness or fits in 9 cases, with field defect or impairment of vision in 5, psychiatric symptoms in one, endocrine disturbances in 2, subarachnoid haemorrhage in 3 cases of angioma, and the external appearance of tumour in 2 cases of heterotopic nasal glioma.

The relative importance of the symptomatology, the ophthalmological findings, and the electroencephalographic and radiological findings varied according to the nature and site of the tumour. It is stated that midline tumours in the posterior part of the middle fossa are the most difficult to diagnose. The type of tumour was glioma in 18 cases, meningioma in 2, pinealoma in 2, dysembryoplasia in 16, and hydatid cyst in 6. In the authors' experience the results of surgery in supratentorial tumours are better than in tumours of the posterior fossa. In the present series there were 8 operative deaths, 7 patients had a recurrence of tumour and died later (with an average survival period of 3 years), and 25 patients are still alive (after an average follow-up period of 4½ years); the remaining 4 patients could not be traced. *J. MacD. Holmes*

1437. **The Prognosis of Haemorrhage from an Aneurysm at the Base of the Brain Treated Conservatively.** (Zur Prognose des blutenden Aneurysma der Gehirnbasis bei konservativer Therapie)
M. KLINGLER. *Schweizerische medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **87**, 1389–1392, Nov. 16, 1957. 14 refs.

In 8¾ years 55 cases of proven subarachnoid haemorrhage due to bleeding from berry aneurysms at the base of the brain were admitted to the Medical or Neurosurgical Clinics of the University of Basle, of which 15 were treated surgically and 40 were not, or could not, be operated on. Of the latter patients, 37 died, 15 within 48 hours of admission and a further 12 within the first week. In 26 of the cases angiography was not performed, either because the patient rapidly succumbed or because of advanced age (5 were over 70 years old) or poor general condition. These figures are similar to those of other authors and demonstrate the need for prompt and active measures if a higher proportion of these frequently young and previously healthy patients are to be saved.
G. S. Crockett

1438. **Arteriovenous Malformations of the Brain and Their Effect upon the Cerebral Vessels**
J. CARRASCO-ZANINI. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **20**, 241–249, Nov., 1957. 13 figs., 11 refs.

The effect of cerebral arteriovenous malformation upon other cerebral arteries and veins was studied at the National Hospital, Queen Square, London, in arteriograms from 102 proved cases of angioma, including 15 in which the malformation had been partially or completely removed. Secondary dilatation of the afferent artery was observed in 95 of the cases. Dilatation was also seen in arteries distal to it, including those as near to the heart as the common carotid and the vertebral arteries. The cortical veins draining the corresponding areas of the angioma were dilated in 70 cases, and the deep venous system was involved in 18. The calibre of adjacent arteries was reduced, and in some cases there was no contrast medium in these vessels. This arterial and venous dilatation disappeared after the angioma had been removed, and the circulation in the unfilled arteries improved, especially in the anterior cerebral artery when the angioma was fed by the middle cerebral artery. The author suggests that further studies should be carried out to assess the full effect of these vascular malformations upon the heart and the systemic circulation. *I. Ansell*

1439. **Neurological Manifestations in Haemangioma of the Vertebrae**
H. ASKENASY and A. BEHMOARAM. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **20**, 276–284, Nov., 1957. 4 figs., 18 refs.

Over a recent 6-year period 8 cases of haemangioma of the vertebrae with neurological manifestations have been seen at the Beilinson Hospital, Petah Tikva, Israel. In 3 cases there were symptoms only, which simulated nephrolithiasis, prolapsed disk, cholelithiasis, pancreatitis, and peptic ulcer, root involvement being considered responsible. Haemangiomata were found incidentally on *x*-ray examination of the spine at levels from D9 to L4. Irradiation of these areas gave symptomatic relief. In 5 cases there were symptoms and also signs of a root lesion or of cord compression, or both. Decompressive laminectomy followed by radiotherapy was carried out in 4 cases after myelography had revealed blocks at various levels between D3 and L2. In one case a subperiosteal haemangioma was removed, with complete recovery. The authors consider that the neurological complications are not due solely to compression, but are worsened by congestion, haemorrhage, and thrombosis within the lesion in combination with stasis of blood flow in the epidural venous plexus and secondary disturbances of the cerebrospinal fluid circulation.
I. Ansell

Psychiatry

1440. **The Action of Autonomic Drugs on Normal Persons and Neuropsychiatric Patients**

R. NELSON and E. GELLHORN. *Psychosomatic Medicine* [*Psychosom. Med.*] **19**, 486–494, Nov.–Dec., 1957. 2 figs., 32 refs.

An investigation was carried out at the University of Minnesota Hospitals, the Minneapolis General Hospital, and two Minnesota State Hospitals, into the action of hypotensive and hypertensive drugs upon sympathetic and hypothalamic reactivity, with particular reference to the possible effect of age on autonomic reactivity and to the differences in reactivity between normal persons and neuropsychiatric patients.

The experimental subjects consisted of 104 individuals (46 males and 58 females) presumed to be normal and 236 neuropsychiatric patients (127 males and 109 females); approximately half of the latter group were suffering from schizophrenia and the remainder from a variety of conditions including psychopathic and other personality disorders, psychoneurosis, and manic-depressive and involutional psychoses. Methacholine ("mecholyl") was regarded as the best hypotensive drug for experimental use and its effect [in unspecified dosage] upon systolic blood pressure was determined in all the subjects, who were classified in three groups, I, II, and III, according to the degree of hypotension induced by the drug and of the subsequent hypertensive "rebound", Group I containing those who showed the maximum hypertensive rebound and Group III those in whom the hypotensive response was predominant. The response of the blood pressure to methacholine is considered to be determined by the excitability of the sympathetic division of the posterior hypothalamus, so that Group I represented sympathetic hyperreactors and Group III sympathetic hyporeactors. Noradrenaline was selected as the most convenient hypertensive drug and the effects of 0·005 mg. injected intravenously on systolic blood pressure and heart rate were determined in all subjects, close attention also being paid to its pulse-slowing effect, as this was regarded as an indicator of parasympathetic reactivity to the drug. In assessing the effect of this drug in each case the "parasympathetic index" (P.I.) was calculated by dividing the maximum rise in systolic blood pressure by the maximum diminution in heart rate.

It was found that the autonomic response to both drugs diminished progressively with increasing age in both the normal subjects and the neuropsychiatric patients. From this the inference is drawn that forms of treatment which act at the sympathetic–hypothalamic level can be expected to be most effective in younger patients. Electric convulsion therapy, which promotes sympathetic responsiveness, would be expected to be most beneficial in those subjects who show a marked hypotensive response to methacholine (Group III), and this is in agreement with clinical experience. Conversely, carbon dioxide therapy, which has been shown to diminish the reactivity of the sympathetic division of the hypothalamus, is most suitable for the treatment of sympathetic hyperreactors (Group I), and is contraindicated in the case of sympathetic hyporeactors (Group III). Variations in the P.I. were too great to permit the recognition of any differences between the two groups. Comparison of the responses to methacholine, however, showed that at all ages members of Groups I and III together were in the majority in the group of mental patients, whereas those of Group II were in the majority in the control group. No sympathetic hyporeactors (Group III) were found among control subjects or patients with psychopathic personality aged 25 and less, whereas of the 13 schizophrenics in this age group, 4 were placed in Group III.

A. Balfour Sclare

1441. **An Investigation of the Medical and Social Needs of Patients in Mental Hospitals. I. Classification of Patients According to the Type of Institution Required for Their Care**

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With the object of providing information which might be of value in the future planning of hospital services for the mentally sick, the authors classified 3,555 patients in mental hospitals in Birmingham (all Birmingham residents) according to their medical, nursing, and social needs. The sample was considered to be reasonably representative, in status, age, and duration of stay, of the mental hospital population of England and Wales. Approximately 13% of patients needed active medical treatment or investigation and 42% required maintenance drug therapy; no medical treatment was needed by the remaining 45%. Skilled nursing was required by 13% and basic personal service only by 23%; no call on nursing services apart from supervision was made by 64%. More than 80% were fully ambulant, but one in 7 was incontinent. Only 1·2% needed close supervision because of aggressiveness or suicidal tendencies, while 14% did not require any supervision. About one-third were incapable of work of any sort; one-quarter could do productive work of benefit to the community in wards, kitchens, and gardens; and one-tenth could undertake light tasks in the wards. One-third were fit for occupational therapy.

Classification of the patients according to the type of facilities required showed that 13% needed full hospital care, 75% limited hospital facilities only, and 12% needed none of the services usually associated with hospitals, only a home or hostel with opportunities for productive work.

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1442. **The Intellectual and Social Status of Children of Mental Defectives**
M. W. G. BRANDON. *Journal of Mental Science* [*J. ment. Sci.*] **103**, 710–724 and 725–738, Oct., 1957. 1 fig., bibliography.

In the first of these two studies the author tested the intelligence of 70 out of 73 mothers who had been in the Fountain Hospital, London (a hospital for mental defectives) and found their average I.Q. to be 73·5. The Terman–Merrill test gave a mean I.Q. of 61·1, whereas the full Wechsler–Bellevue test gave a mean score of 83·1 and the Progressive Matrices test a mean of 81·1; for the 40 mothers tested on both the Terman–Merrill and the Wechsler–Bellevue scales the means were 63 and 83 respectively. Of the 73 mothers, 36 suffered from one or more physical handicaps, and 67 from emotional, 14 from educational, and 11 from economic handicaps. Of 65 mothers discharged at various times up to 14 years previously (mean nearly 5 years), 27 were employed and 26 were working at home as married women. Assessment on a 5-point scale (maximum score 5) of 63 of the patients in their capacity as " mothers ", " wives ", or " housewives " showed that 20 were rated as mothers with a mean score of 3·3, 22 as wives with a mean of 3·3, and 21 as housewives with a mean of 3·1. It is concluded that women with an I.Q. of 50 and over on the Terman–Merrill scale or of 70 and over on the Wechsler–Bellevue scale are capable of bringing up children and running a home. [As most of the mothers were sent to the Fountain Hospital from other mental deficiency hospitals, the author argues that they were similar to those in other hospitals. This is not necessarily true as the other hospitals may have selected a certain type of mother to send to the Fountain Hospital.]

In the second part of the study, which was carried out on 74 of the 109 living children (out of 150) of these mothers, various different intelligence tests were administered on 119 occasions, the score in the test best suited to the child's age or the average of the scores in different tests being used for each child. By the former method the mean of the scores was 89·1 and by the latter it was 90·5. A third method, in which the scores obtained by the first method were converted to the same S.D., gave a mean of 89, and by a fourth method, in which the highest score in any test was taken for each child, the mean was 93·7. Of the 109 children alive, only 14 had been dealt with under the Mental Deficiency Acts, an additional 4 being in schools for the educationally subnormal. Of the total of 150 children, 120 (80%) were illegitimate. The mean I.Q. of 30 children brought up by their own mother was 98·7; that of 25 brought up by a 1st or 2nd foster mother or close relation was 96·8; and that of 38 brought up in orphanages or by a series of foster mothers was 87·6. There were 34 children over the age of 16 years, 24 being at work.

In 77 cases the coefficient of correlation between the I.Qs of the mother and child on the Terman–Merrill scale was 0·14, and in 65 cases on the Wechsler scale it was 0·008. The less intelligent mothers appeared to produce more of the defective children than did the more intelligent, although no definite correlation was found between the scores of the children and those of the parents (including 54 of the fathers). In 18 cases the mother had a sibling who had been certified as feeble-minded; the mean I.Q. of these mothers was 76 and of their children it was 89, these figures differing little from the mean for the whole group. The children's intelligence showed a regression towards the mean, their I.Q. points varying from 30 to 132, a range of 102, whereas that of their mothers varied from 43 to 113, a range of 70. It is noted that feeble-minded women " do not appear to have large numbers of defective children ", the proportion in the present survey being only 3·7%.

G. de M. Rudolf

1443. **Fractionated Encephalography in Schizophrenic Syndromes.** (L'encéphalographie fractionnée dans les syndromes schizophréniques)
P. BORENSTEIN, M. DABBAH, and J. METZGER. *Annales médico-psychologiques* [*Ann. méd.-psychol.*] **2**, 385–426, Oct., 1957. 9 figs., 40 refs.

The results of a study of 134 cases of schizophrenia by Lindren's method of fractionated air encephalography are reported and the technique described in some detail. Only 16 normal encephalograms were obtained in the whole series. The most frequent finding was cortical atrophy, which in most cases was limited to the frontal and parietal lobes. Dilatation of the third ventricle and the temporal horns of the lateral ventricles was also found. The patients' ages ranged from 17 to 60 years, and the radiographic findings are tabulated in relation to age (in 5-year groups), to age at onset of the schizophrenic symptoms, and to duration of symptoms. The incidence of cortical atrophy was shown to increase with age and with the duration of symptoms.

An interesting finding was that the ventricles were small in 17% of cases, but this phenomenon was not observed in patients under the age of 20 or over the age of 50 years; the highest incidence (33%) was in the age group 20–25, the over-all incidence being about equal in the various types of schizophrenia. The authors suggest that these radiological changes, although they are found in other mental syndromes and are not specific for schizophrenia, may lead one step nearer to the " organic basis " of the schizophrenic syndrome envisaged by Bleuler.

J. MacD. Holmes

1444. **Treatment of Alcoholism by Intravenous Infusions of Sodium Thiosulphate.** (Опыт лечения алкоголизма внутривенными вливаниями тиосульфата натрия)
B. M. SEGAL and G. M. HANLARJAN. *Журнал Невропатологии и Психатрии* [*Z. Nevropat. Psihiat.*] **57**, 1242–1247, No. 10, 1957. 1 fig., 37 refs.

Among the various metabolic disturbances found in severe chronic alcoholics are abnormalities of the metabolism of heavy metals. The rationale of the use of sodium thiosulphate in counteracting these is discussed. In addition to this action sodium thiosulphate also creates a temporary " sensitization " to ingested alcohol, with autonomic nervous disturbances similar to those produced by " antabuse " (disulfiram).

This latter effect was used by the authors to establish a " negative conditioned reflex " to alcohol in the treat-

ment of 78 patients with severe chronic alcoholism, most of whom had previously been unsuccessfully treated with apomorphine and by other methods. A course consisting of 7 to 10 intravenous injections of 15 to 25 ml. each of a 30% solution of sodium thiosulphate was given, one injection a day to patients in hospital and 2 per week to others, this being followed by 3 or 4 further injections at 10-day intervals. Withdrawal symptoms generally decreased markedly after 2 to 4 injections, and the craving for alcohol also diminished. Later in the course 4 or 5 "provocation" doses of alcohol were given, these being administered soon after the thiosulphate injection in order to produce the greatest reaction. In 25 (32%) of the 78 cases the patient failed to respond, but in the remainder a remission of at least 4 to 5 months was obtained. In a control group of 78 similar patients treated with apomorphine the proportion failing to respond was also 32%, but the remissions among the remainder were of shorter duration. Advantages of the thiosulphate treatment are the absence of any toxic effects, and that the drug can be safely given in the presence of somatic diseases such as hepatitis, hypertension, and toxic psychoses. *Alexander Duddington*

1445. **Chlorpromazine Therapy following Transorbital Lobotomy**

W. H. PATE. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **125**, 44–50, Jan.–March [received Dec.], 1957. 12 refs.

A controlled study of the effect of chlorpromazine in long-standing psychosis which had not responded to transorbital lobotomy was carried out at DeWitt State Hospital, Auburn, California, on 100 chronically ill patients—mostly schizophrenics, but including also involutional, senile, and manic-depressive psychotics—who had been in a mental hospital for more than 10 years.

The patients were divided into 5 groups of 20 as follows: Group 1, patients who had responded unsatisfactorily to transorbital lobotomy performed one month to 6 years previously; Group 2, controls, comparable to the patients in Group 1; Group 3, patients in whom lobotomy was indicated but could not be performed; Group 4, controls comparable to the patients in Group 3; and Group 5, patients recently subjected to lobotomy. Groups 1, 3, and 5 received chlorpromazine (the last group 5 to 7 days postoperatively) in a dosage initially of 25 mg. intramuscularly twice daily, this dosage being increased by 25 mg. daily to 200 mg., when it was reduced at the same rate as it was increased and chlorpromazine by mouth substituted. Thus on the 12th day the patients were receiving chlorpromazine by mouth only. It was found ultimately that most patients responded satisfactorily to a dosage of 300 to 600 mg. daily by mouth. Some of the patients in Group 5 required, in addition to an oral dose of chlorpromazine of 50 to 500 mg., an occasional course of intramuscular injections of 100 mg. once or twice daily for 2 to 3 days.

Of the 60 patients in Groups 1, 3, and 5, 54 improved after administration of chlorpromazine for at least 2 months, 20 being out of hospital after one year and 13 being able to earn their own living. Of the 40 patients in the two control groups, who did not receive chlorpromazine but continued previous treatment, including electric convulsion therapy, hydrotherapy, sedation, and administration of reserpine, only one showed some improvement after 6 months.

Side-effects, which were few, included painful inflammation at the site of injection; transitory orthostatic hypotension in a few patients who got out of bed too soon after the injection; a distressing dermatitis (in 3 cases) which resembled urticaria, especially in areas exposed to light, but which tended to disappear after a short interval without chlorpromazine; and in several cases symptoms of Parkinsonism which subsided when the dosage of chlorpromazine was reduced. Lethargy and drowsiness were counteracted by concurrent administration of dexamphetamine sulphate. *F. K. Taylor*

1446. **The Use of Reserpine in Autistic Children**

E. LEHMAN, J. HABER, and S. R. LESSER. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **125**, 351–356, July–Sept., 1957 [received Jan., 1958]. 13 refs.

From King's County Hospital (State University of New York) are reported the results of treatment with reserpine of 7 boys and 2 girls aged between 3½ and 9 years, all of whom were markedly autistic; 4 of the patients had failed to respond to previous treatment at a "schizophrenic nursery", and 5 had no speech. A psychiatric 6-point rating scale in respect of 22 functions was used to record the status of the children. In 7 cases in which the children were in a day nursery independent reports of the nursery staff were obtained. Reserpine was given initially in a dosage of 0·2 mg. three times a day, this being gradually increased until the optimum dose was found for each child. Some time after this had been established the drug was suddenly replaced by a placebo and the effects noted.

The optimum dose, which ranged from 3 to 7 mg. daily, produced some tranquilization in every case, the children becoming easier to manage and going to bed and to sleep earlier. In addition all the children showed some progress in emotional maturation under reserpine therapy, this being more marked in the younger patients; thus 5 children with an initial rating of 6 (severest disorder) improved to 5, and the other 4, originally rated 5 or 4, improved by one or two ratings. The improvement was manifested in an increased awareness of reality, an improved pattern of play, and a better appetite. Side-effects in the form of nasal obstruction, dryness of the mouth, and somnolence appeared in some children given optimal dosage, but were temporary. In 4 children given larger doses toxic symptoms developed, these resulting in hyperactivity, enuresis, dribbling of urine, and frequency of micturition; these manifestations disappeared when the dose of the drug was lowered. When the drug was replaced by a placebo 2 children developed a withdrawal syndrome which took the form of hyperactivity and ultra-severe psychotic symptoms, but resolved when reserpine was again administered. It is concluded that treatment with reserpine may make possible psychotherapy and even some education of the autistic child. *E. H. Johnson*

Paediatrics

NEONATAL DISORDERS

1447. **Comparison of Ocular Reaction Using Penicillin and Bacitracin Ointments in Ophthalmia Neonatorum Prophylaxis**

A. M. MARGILETH. *Journal of Pediatrics* [*J. Pediat.*] **51**, 646–651, Dec., 1957. 19 refs.

A comparative study of the effects of instillation of silver nitrate solution, penicillin, and bacitracin into the eyes of newborn infants was undertaken in the Pediatric Service of the U.S. Naval Hospital, Corona, California. After instillation of silver nitrate in a 1% solution there was swelling of the eyelids with purulent discharge from the eyes in about 50% of infants so treated. Of 5,394 newborn infants whose eyes were treated with penicillin (either in a solution of 5,000 units per ml. or in an ointment containing 1,000 units per gramme), 50 had mild and 9 had moderate reactions; there were no severe reactions to this treatment. Follow-up examinations during the first 2 weeks of life showed that 3·2% of infants developed eye infections. Bacitracin ointment (500 units per gramme) was applied to the eyes of 2,380 newborn infants; 16 developed mild and 5 moderate reactions but none showed severe reactions. Up to the 14th day of life 1·6% of the infants in this group had developed eye infections. When the number of children with local reactions was added to the number developing infection it was found that 4·2% of the penicillin-treated group and 2·3% of those given bacitracin were affected, a difference which is not statistically significant. The author concludes that specific chemotherapy should not be employed as a routine to prevent the development of ophthalmia neonatorum, but that infections should be treated when they arise. Bacitracin appears to be a safe, effective, and relatively non-irritant agent if chemoprophylaxis is considered desirable. *R. M. Todd*

1448. **Erythema Neonatorum Allergicum. A Study of the Incidence in Two Hundred Newborn Infants and a Review of the Literature**

W. B. TAYLOR and C. P. BONDURANT. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **76**, 591–594, Nov., 1957. 2 figs., 13 refs.

Erythema neonatorum allergicum is defined as a dermatitis occurring in the newborn infant in the first 3 days of life and consisting in erythema and papules with, in about 10% of cases, the formation of pustules. The rash, which usually disappears by the 6th day, may occur anywhere; the commonest site is on the anterior trunk, but the back, face, and extremities are also frequently affected. When pustules do occur they are sterile and contain over 90% eosinophil granulocytes, in contrast to the predominance of neutrophils in pyodermic lesions. The condition seems to have been well known to obstetricians over many centuries and the related literature is discussed. The distribution of the condition appears to be world-wide and presents no particular geographical, racial, or seasonal variation. The disorder may be of very brief duration, with the result that the reported incidence has varied from 4·5% (of 1,649 births) to 72% (of 228 births).

In the present study the authors observed daily 200 consecutive infants born at St. Joseph's Mercy Hospital, Ann Arbor, Michigan, during a 3-month period in 1956. Of these, 62 (31%) had erythema neonatorum allergicum during their stay; a further 13 (6·5%) showed what was considered to be physiological postnatal redness, 32 (16%) had scratches and abrasions, and 9 (4·5%) had simple dryness and scaling. Almost all the cases of erythema neonatorum allergicum developed by the 2nd day of life and the duration was 3 days or less in more than 90% of the affected infants. Three different ointments were applied to the skin of the newborn at this hospital, but the distribution of the cases of erythema neonatorum allergicum or its severity bore no relation to the use of any one of these medicaments nor did it differ from that in a control group of similar infants not so treated. *Benjamin Schwartz*

1449. **Congenital Hemolytic Anemia in the Newborn. Relationship to Kernicterus**

C. C. STAMEY and L. K. DIAMOND. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **94**, 616–622, Dec., 1957. 1 fig., 26 refs.

Attention is drawn in this paper to the appearance of jaundice within the first 48 hours of life in babies born into families known to be affected by congenital haemolytic anaemia. Four such cases are described in which the main findings were jaundice with increasing hyperbilirubinaemia, increased osmotic fragility of the erythrocytes, spherocytosis, and minimal splenomegaly. In 2 cases there was a rapidly rising indirect-reacting bilirubin level in the serum without anaemia. The result of the direct Coombs test was negative and evidence of blood-group incompatibility was lacking in all cases. The only treatment given was exchange transfusion, which was repeated in one case to control the serum bilirubin level. The authors have not encountered the overwhelming infections which have been reported to occur after splenectomy in infants with congenital haemolytic anaemia, but they would not in any event advise operation at this age if the disease is well compensated.

Out of a series of 52 proven cases of hereditary spherocytosis in children between the ages of one week and 10 years admitted to the Children's Medical Center, Boston, during the past 10 years, an adequate neonatal history was available in 43; 23 of these infants became jaundiced within the first few days of life. Although kernicterus apparently did not occur in this group, one case which was considered to be due to hereditary spherocytosis

has been reported by Roddy (*J. Pediat.*, 1954, **44**, 213). The authors stress that the offspring of a parent with hereditary spherocytosis should be treated like the infant of a sensitized Rh-negative mother, hyperbilirubinaemia being controlled by exchange transfusion.

A. White Franklin

1450. **Haemolytic Disease of the Newborn. The Fate of 246 Rhesus-incompatible Pregnancies**

G. A. KELSALL, J. R. H. WATSON, and G. H. VOS. *Lancet* [*Lancet*] **2**, 1255–1258, Dec. 21, 1957. 9 refs.

Follow-up findings are now reported regarding the outcome of 246 Rh-incompatible pregnancies previously described by two of the authors (Kelsall and Vos, *Lancet*, 1955, **2**, 161; *Abstr. Wld Med.*, 1956, **19**, 153) from the King Edward Memorial Hospital, Subiaco, Western Australia. In 39 cases (16%) the baby was stillborn, and in 21 cases it died within one year. Of the remaining 186 babies, 15 could not be traced, but of 159 (64%) seen at the age of 18 months, 158 were found to be normal and 12 further infants, though not seen, were reported to be healthy. One spastic child was clearly a case of kernicterus.

Attention is drawn to the diagnostic value of a rapidly rising antibody titre as an indication for early induction of labour. In this series the babies born before term did just as well as those born at term, although many of the latter were minimally affected whereas most of the former were suffering from more severe haemolytic disease. These good results are attributed to the use of fresh heparinized blood of the same ABO group as the baby and Rh type as the mother. The volume of blood transfused ranged from 150 to 250 ml. per lb. (330 to 550 ml. per kg.) body weight, in 50-ml. volumes, using a 50-ml. syringe and leaving a positive balance. The authors state that " if the infant is watched antenatally, delivered when indicated, and adequately treated postnatally, very few retarded or imbecile children need be expected ".

[No comment is made upon the prevention of kernicterus by bilirubin control.] *John Murray*

1451. **Excess of Group O-Mothers in ABO-Haemolytic Disease.** [In English]

G. MUNK-ANDERSEN. *Acta pathologica et microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **42**, 43–50, 1958. 2 figs., 15 refs.

In investigations on a number of umbilical cord sera of ABO-compatible mother–child combinations it was found that A_2-mothers generally produce a stronger incomplete anti-B which is able to pass the placenta than do A_1-mothers, and that it is almost as strong as the anti-B found in O-mothers. In a series of 45 newborn infants whose red cells were demonstrably sensitized by ABO-antibody it was found that 43 of the mothers were of Group O and 2 of Group A. Both A-mothers were of Group A_2; considering the findings mentioned above, it is thought that this can hardly be a chance finding. Thus not only the excess of O-mothers demonstrated by Rosenfield, but an excess of $O+A_2$-mothers were found.

In examinations of eluates from red cells of 34 children of O-mothers the hypothesis put forward by Wiener and co-workers that ABO-haemolytic disease should generally be caused by cross-reacting antibody could not be confirmed. Assuming that cross-reacting ABO-antibody may have a very different affinity to A- and B-cells this hypothesis could not be refuted either. But it is pointed out that it requires further elaboration if it is to explain in full the excess of O- (and A_2-) mothers in ABO-haemolytic disease.—[Author's summary.]

1452. **Measurement of Fetal Hemoglobin in Newborn Infants. Correlation with Gestational Age and Intrauterine Hypoxia**

C. D. COOK, H. R. BRODIE, and D. W. ALLEN. *Pediatrics* [*Pediatrics*] **20**, 272–278, Aug., 1957. 5 figs., 17 refs.

The relationship between the amount of foetal haemoglobin present at birth, the gestational age of the infant, and the occurrence of intra-uterine hypoxia was studied at the Lying-in Hospital, Boston, in 152 infants of gestational age 25 to 44 weeks, the foetal haemoglobin content of cord blood being estimated by the technique of denaturation by alkali. In 27 of 29 infants of less than 36 weeks' gestation over 90% of the haemoglobin was of foetal type. At 39 weeks' gestation the mean proportion of foetal haemoglobin was 82%, at 41 weeks it was 77%, and at 43 weeks 69%. The authors state that this decrease in foetal haemoglobin after the 34th week " is similar to the 3% to 4% decrease described for each post-natal week ". Thus the change from foetal to adult haemoglobin is related to the age of the infant from conception and is not affected by the change from intra- to extra-uterine existence.

There was no evidence of increased foetal haemoglobin in post-mature or hypoxic infants. It is suggested that the increased total concentration of haemoglobin in post-mature and hypoxic infants is possibly the result of haemoconcentration. *John Murray*

CLINICAL PAEDIATRICS

1453. **Head Injuries in Childhood**

P. HARRIS. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **32**, 488–491, Dec., 1957. 3 figs., 9 refs.

The main features of head injuries in childhood are discussed with reference to 150 consecutive children with such injuries seen at the Royal Infirmary, Edinburgh, in the 5-year period 1950–4. The injuries were mild, usually without residual neurological abnormalities in 61 of the children and severe in the remainder. There was a striking preponderance of males in the series, the ratio being 3:1. In 56 cases the injuries were sustained in traffic accidents, in 37 they were due to a fall, and in most of the remainder they were the result of direct blows to the head.

Linear, diastatic, and, in particular, compound fractures were often seen, but basal fractures of the skull were uncommon. Of 11 children in whom extradural haematomata were found, 4 died; in each instance there had been delay in instituting treatment. The history of

extradural haematoma was briefer than that obtained in adults, and there was often no initial period of unconsciousness. The total number of deaths in the series was 15. As regards sequelae, post-traumatic epilepsy occurred in 39 of the patients, and in 20 there were psychological changes, which were persistent in half of them. The author emphasizes that careful assessment of possible psychological changes is necessary in all these cases, otherwise serious disabilities may go unnoticed with consequent difficulties, for example, during education of the child. Dysphasia was observed in 12 children and persisted to an important degree in 4. An interesting finding was that if damage to the left cerebral hemisphere occurred before the age of 2 years, the child might become left-handed and develop normal speech. Other neurological abnormalities, principally varying degrees of hemiparesis, were noted in 27 of the patients.

R. G. Rushworth

1454. **Spontaneous Dislocation of the Cervical Spine in Childhood**

R. M. I. MACKAY. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **32**, 505–507, Dec., 1957. 3 figs., 2 refs.

In this paper from the Royal Hospital for Sick Children, Edinburgh, the author reports spontaneous dislocation of the cervical spine in 10 children aged 1½ to 10 years, all the cases being seen within a period of 11 years. Of the 10 children, 9 had cervical adenitis and one pharyngitis. The cause of the dislocation is believed to be hyperaemia of the retropharyngeal tissues and vertebral ligaments, so that the latter are weakened and thus allow spontaneous dislocation to occur.

Usually there was a history of painful stiff neck and torticollis, the duration of these symptoms varying from one day to 3 weeks. All the patients walked into hospital, and in none of them was any neurological abnormality demonstrable. The dislocation could be seen in a lateral radiograph, but no disease of the vertebral bodies themselves was revealed. In 8 cases the second cervical vertebra had slipped forward on the third, in one case the third had slipped forward on the fourth, and in the remaining case there was subluxation of the atlas. Reduction was effected by slight hyperextension of the neck, obtained by placing a low pillow under the shoulders and maintained with head-halter traction with a weight of one pound (0·45 kg.). When the pain, spasm, and inflammation had subsided, movement in bed was permitted in mild cases. If there was a long history, or the infection was severe, a collar was fitted. The end-result was satisfactory in all cases, without recurrence.

R. G. Rushworth

1455. **Congenital Idiopathic Hypertrophy of the Heart in Children.** (О врожденной идиопатической гипертрофии сердца у детей)

G. M. KAZAKEVIČ. *Педиатрия* [*Pediatrija*] **35**, 60–66, No. 12, Dec., 1957. 16 refs.

Idiopathic hypertrophy of the heart has been recognized for many years as a nosological entity by numerous authors in all countries. The essential feature of the disease is hypertrophy of the heart muscle, but opinions differ as to its nature, some workers attributing it to an increase in the number of fibres and others to an enlargement of the individual fibres, these two types being distinguished as hyperplasia and hypertrophy respectively. There are no pathological changes in the vessels or valves of the heart, no evidence of inflammation, and no extracardial cause to which the hypertrophy can be attributed. In this it differs from fibro-elastosis and idiopathic myocarditis. [The cardiomegaly of von Gierke's disease is not mentioned in the differential diagnosis.]

The condition usually presents as a failure of the systemic circulation, which may develop very rapidly. This, together with the enlarged, spherical heart shadow on radiological examination, is almost diagnostic in a very young child, as congestive failure is rare in congenital valvular heart disease. The sternum is prominent, the lungs are congested, and in 3 out of the 4 cases described by the author pneumonia was diagnosed during life; in one case this was confirmed post mortem, in one numerous pulmonary infarcts were present, and in one there were patches of atelectasis. The heart sounds are rapid, there is often arrhythmia, and murmurs, usually systolic, may be present. In spite of treatment all the author's 4 patients succumbed within 3 weeks of admission—in one case within 2 hours.

L. Firman-Edwards

1456. **ABO Blood Groups and Bronchopneumonia in Children**

C. CARTER and B. HESLOP. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **11**, 214–216, Oct., 1957. 4 refs.

It has been established that a relationship exists between ABO blood groups and the incidence of certain diseases of the upper alimentary tract. In 1951 Struthers suggested, on the basis of 400 consecutive post-mortem examinations in a Glasgow hospital, that children of Blood Group O are relatively resistant to bronchopneumonia. He found that of 55 children in whom there was no abnormality at death except bronchopneumonia, 14 had Group-O blood; of 93 children who had bronchopneumonia and some other abnormality, 33 had Group-O blood; and of a large control group of children, 51% had Group-O blood.

The present authors, at the Hospital for Sick Children, Great Ormond Street, London, examined lung sections from 358 children whose blood group had been determined. For various reasons these were not from consecutive necropsies, of which 964 were performed during the period (1949–55). It was found that Struthers's experience in Glasgow could not be repeated, because all the children in the authors' series had other abnormalities associated with the bronchopneumonia. In addition, only 45·8% of a control group of children in London had Group-O blood. The percentage of children in London with Group-O blood suffering from bronchopneumonia was 40·35, a finding which did not confirm the previous observation.

The authors point out there is still need for further investigation of this problem, since the degree of association differs in different areas.

J. G. Jamieson

Public Health and Industrial Medicine

PUBLIC HEALTH

1457. **An Investigation of the Growth of Children at an Open Air School**
W. H. HAMMOND and J. A. GILLET. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **11**, 217–225, Oct., 1957. 1 fig., 7 refs.

Between June, 1951, and October, 1954, the growth of children attending an open-air school at Rotherham for remedial treatment for a variety of conditions, including general debility, was compared with that of children attending ordinary schools. From the open-air school 127 children aged 7 to 15 were selected on grounds of poor nutrition (nutritional group); all were expected to remain at the school for at least a year. From the ordinary schools two groups were selected—namely, 60 healthy children aged 7 to 15 years attending primary or secondary modern schools in a pleasant part of the town (the control group) and 36 siblings of the children at the open-air school (the sibling group). Some twenty body measurements, including weight, height, and subcutaneous fat, were obtained for each child, weight being ascertained monthly and the majority of the other values determined every 3 months.

In the nutritional group the gain in weight was proportionately less than in the other groups when compared with the gain in height. This was true of both actual weight and the value obtained by subtracting predicted weight from actual weight. [This last calculation is a somewhat complex one which makes allowance for different skeletal framework in different groups.] The findings confirm the view that weight increase is affected by nutritional conditions rather than growth in height.

[This survey also indicates that until there is some accurate method of estimating nutritional standards there are no grounds for supposing that leptosomes are necessarily more undernourished than eurysomes. It is often suggested that thin, lanky children are less healthy than fatter, stockier children, but there does not appear to be any real evidence that this is so.]

J. G. Jamieson

1458. **Observations on Changes in the Physical Development of Children in the U.S.S.R.** (Динамические наблюдения за физическим развитием детей в СССР)
M. D. BOL'ŠAKOVA. *Гигиена и Санитария* [*Gig. i Sanit.*] **23**, 32–38, Jan., 1958. 6 figs., 10 refs.

A survey is presented of the changes which have taken place during the past 20 years in the rates of increase in height, weight, and chest measurement of children in the U.S.S.R. These rates are shown to be related to the general standard of living, and were particularly high in 1938–9, which was a period of good agricultural yields. The average standard of physique and rate of growth of Russian children fell during the period of the Second World War, but the original levels have now been regained and even surpassed.

The average difference in height between boys aged one and 14 years in 1938 was 68·9 cm., in 1943 60·6 cm., and in 1955 70 cm. For girls the corresponding figures were 69·6, 68·2, and 71·1 cm. The average differences in weight between boys of these ages in the same 3 years were 28, 23·2, and 34·3 kg. respectively, the corresponding figures for girls being 30·5, 26·8, and 31·8 kg. Figures for the chest measurement showed similar, though less marked, trends.

Further analysis of the statistics shows that the rate of physical development recovered from the effects of war-time conditions more slowly in younger than in older children. In 1938 the average difference in height between boys of one and 7 years was 45·1 cm., in 1943 it was 41·5 cm., and in 1955 it had still only reached 43.4 cm. Between boys of 9 and 14 years, however, the difference in height, which in 1938 was 23·8 cm., and in 1943 19·1 cm., was 26·6 cm. in 1955. It thus appears that at that time the older children had more than recovered from the effects of war-time conditions, whereas the younger children still had some way to go.

Basil Haigh

1459. **The Care of the Long-term Patient: a Review of the Administration of Present Programs**
E. J. MUNTER and M. BERKE. *Journal of Chronic Diseases* [*J. chron. Dis.*] 7, 144–177, Feb., 1958.

1460. ***Salmonella* Infections in Rodents in Manchester with Special Reference to *Salmonella enteritidis* var. *danysz***
C. M. BROWN and M. T. PARKER. *Lancet* [*Lancet*] **2**, 1277–1279, Dec. 21, 1957. 3 refs.

Although only 4 of the 2,149 *Salmonella* infections in man noted by the Public Health Laboratory, Manchester, in the 7 years 1949–55 were due to the *danysz* variety, 2 such cases in 1953 and one in 1954 were found to be food-borne, and evidence was obtained that the infection had been derived from mice which had acquired the infection from living cultures of the organism employed locally as bacterial rodenticides. It seemed desirable, therefore, to ascertain the carrier-rate of *Salm. enteritidis* var. *danysz* among "normal" wild mice and other rodents in the area.

A total of 256 house mice from the city and 108 from the port of Manchester were examined: *Salm. enteritidis* var. *danysz* was found in one of the former (0·4%) and *Salm. stanley* in 2 of the latter (2·7%). Of 405 brown rats from the city, 14 (3·5%), were infected with salmonellae, 5 of these with *Salm. enteritidis* var. *danysz*, and of 95 brown rats from the port, 8 (8·4%) were infected with salmonellae, 7 of which were of the *dansyz* variety. No positive cultures of salmonellae were

obtained from 279 black rats examined. None of the rats infected with the *danysz* variety had been caught on premises in which a bacterial rodenticide had been used, suggesting that this organism is a natural pathogen of the Manchester brown rat, but it seemed likely that the one infected house mouse had acquired the organism from bait in a nearby bakery. The authors consider that the use of bacterial rodenticides should be prohibited.

F. T. H. Wood

1461. **On the Rise and Decline of Poliovirus Antibodies in Different Human Populations**

G. L. Le Bouvier. *American Journal of Hygiene* [*Amer. J. Hyg.*] **66**, 342–362, Nov., 1957. 5 figs., 26 refs.

The author reports, from Yale University School of Medicine, the results of a study of the relative frequency of "high", "medium", "low", and "undetectable" serum levels of neutralizing antibody against the 3 types of poliomyelitis virus for 8 age groups (up to over 50 years) in 5 different populations, the respective serum dilutions for the 4 categories being over 1:250, between 1:250 and 1:50, between 1:50 and 1:10, and less than 1:10. A total of 5,297 specimens of serum obtained from two different population groups, one richer and one poorer, in each of two American cities (Charleston, West Virginia, and Phoenix, Arizona), in the course of a 3-year survey and 204 specimens from a random sample of a fifth population in the neighbourhood of Cairo, Egypt, were assayed by the panel test method.

Analysis of the data showed that the populations examined formed a graded series in respect of the patterns of rise and decline in the poliomyelitis virus antibody levels with increasing age, and this gradation appeared to be consistent for all 3 types of the virus. In general the lower the standard of hygiene of the particular population, the earlier the age and the faster the rate at which antibodies were acquired, and also the earlier the age at which the proportion of those with high levels of antibody began to decline, this decline of high antibody levels being just as rapid in the population with the lowest standard of hygiene as in that with a higher standard, in which exposure to poliomyelitis was less uniform. After attaining a certain level the percentage of subjects with antibody against all 3 types of the virus and of "residual negative" subjects in a population tended to remain constant, although both the age at which this occurred and the percentage varied from one population to another. The lower the hygienic standards, the smaller appeared to be the percentage of "residual negatives" and the earlier the age at which the residual curve reached an asymptote. To some extent, also, a state of dynamic equilibrium apparently developed between the 3 categories (high, medium, and low) of antibody levels within the positive group. In all the populations studied, high levels of antibody were maintained by more individuals against Type-2 virus than against the other two types.

For the Egyptian population curves indicating the proportion of individuals with the two kinds of complement-fixing antibodies at a serum dilution of 1 : 5 were plotted and were found to run roughly parallel with the curves for those with high levels of neutralizing antibody against the same virus type. Statistical analysis of all the results indicated a measure of significance for the principal features of the patterns of rise and decline of the antibody level in these populations and for the differences between one population and another. The results seem to indicate that the retention of high levels of antibody in the serum is not essential to the maintenance of the high immunity apparent in older age groups.

A. Ackroyd

1462. **Presence of Children in the Household as a Factor in the Incidence of Paralytic Poliomyelitis in Adults**

M. Siegel, M. Greenberg, and J. Bodian. *New England Journal of Medicine* [*New Engl. J. Med.*] **257**, 958–965, Nov. 14, 1957. 4 figs., 38 refs.

Analysis of the data of a clinical and epidemiological investigation of 1,299 cases of poliomyelitis occurring in adults between 15 and 44 years old reported to the City of New York Health Department between 1949 and 1953 inclusive revealed that the average annual incidence of paralytic poliomyelitis was higher in males than in females at all ages up to 20 years. Beyond this age the incidence in the sexes was comparable except in the age group 25 to 29, in which it was significantly higher in women. This appeared to be due, in part at least, to the large number of pregnant women in this age group.

For all the different categories considered (males, single and married women, and pregnant and non-pregnant women) the rate of paralytic poliomyelitis was higher in households with children than in those without. Also married non-pregnant women had a significantly higher rate than single women in households with or without children; in households with children the paralytic rate among pregnant married women was significantly higher than the rates in men and single and non-pregnant women. The rate for pregnant women was 2 to 3 times as high in households with children as in those without, whereas the rates for men and non-pregnant women were only about one-third higher in households with children. Thus a pregnant woman in a household with children runs the greatest risk, and a single woman without household contact with children the least risk.

A. Ackroyd

1463. **Vaccination and the Decline in Paralytic Poliomyelitis**

E. H. Lossing. *Canadian Journal of Public Health* [*Canad. J. publ. Hlth*] **48**, 449–453, Nov., 1957. 5 figs., 2 refs.

The annual number of reported cases of paralytic poliomyelitis in Canada increased from 284 in 1950 to 3,691 in 1953; thereafter the number fell each year to 368 cases in 1956. An examination of the combined notification rates for 8 of the provinces for different age groups shows that in each of the 3 years 1952, 1953, and 1954 the maximum incidence occurred in the age group 5 to 9 years, and that although the general level of incidence differed in the 3 years, being highest in 1953 and lowest in 1954, the age distribution of the cases notified in each year remained much the same. In 1955 and 1956 the maximum incidence had shifted to the preschool age group, 0 to 4 years. The age-specific notifica-

tion rates for 1956 were consistently the lowest of the whole period since 1950, and those for 1955 were lower than in earlier years except for one age group (30 to 34 years). The shift of the maximum notification rate from 5 to 9 years in 1952–4 to 0 to 4 years in 1955–6 is confirmed by examination of the data in various other ways, and additional evidence is presented that this shift was probably due to a selective reduction in the incidence of the disease in the age group 5 to 9 years, there being fewer cases in 1956 in this age group than would have been expected from past experience.

The poliomyelitis vaccination programme in Canada began in April, 1955, and by the beginning of the 1956 poliomyelitis season about 1·8 million children had been vaccinated, about 90% of these having received two doses. Very little vaccination was carried out in the summer of 1956. The majority of the children vaccinated were of primary-school age by 1956. The author therefore concludes that " it would seem reasonable to infer that the relative lack of paralytic cases which has been demonstrated in the vaccinated ages is the reflection of the protective effect of the vaccine program ". He stresses, however, that the possible " natural " immunizing effect of the heavy epidemic of 1953 should not be overlooked. *E. A. Cheeseman*

1464. **Combined Immunization against Diphtheria and Whooping-cough in Infants Aged 2–5 Months**
G. BOUSFIELD. *British Medical Journal* [*Brit. med. J.*] 2, 1216, Nov. 23, 1957. 2 refs.

Experience has shown that the risk of provoking poliomyelitis by immunization against diphtheria and whooping-cough is much less at the age of 3 to 6 months than in older children, but doubts have been expressed as to the effectiveness of immunization at such an early age. The author here gives a preliminary report on the results of immunization of 1,641 infants aged 2 to 5 months, of whom 941 gave a positive and 700 a negative Schick reaction before inoculation. Each was given 3 injections at monthly intervals of 30 Lf of diphtheria toxoid mixed with 10,000 million *Haemophilus pertussis* organisms. When the Schick test was repeated 15 months later 99·7% gave a negative reaction. A further test was performed on 148 of the children at an average age of about 4¾ years, when a negative reaction was obtained in 93·9%. It is suggested that " the above data should dispose, once and for all ", of the idea that immunization against diphtheria at a very early age is unreliable.
Franz Heimann

1465. **The Epidemiology of Acute Respiratory Illness. I. Observations on Adenovirus Infections Prevailing in a Group of Families**
H. A. WENNER, G. W. BERAN, J. WESTON, and T. D. Y. CHIN. *Journal of Infectious Diseases* [*J. infect. Dis.*] **101**, 275–286, Nov.–Dec., 1957. 4 figs., 20 refs.

A study was made to delineate the role of adenoviruses as the cause of minor respiratory illnesses occurring in 88 families resident in Fort Leavenworth, Kansas. Two Type-2 and two Type-3 adenoviruses were recovered from the respiratory tracts of children. Seroconversion rates against Type-2 and Type-3 adenoviruses for children up to 15 years of age approximated 20%. Conversion against adenovirus Type 5 was also observed, but the emergence of Type-5 antibodies during Type-2 and Type-3 infections and the failure to recover Type-5 virus casts doubt on the specificity of the response. The rate of acquisition of antibodies to adenoviruses within the family unit varied, being quite high and apparently occurring quite rapidly with adenoviruses Types 2, 3, and 5, and quite slow to inapparent with Types 1, 4, 6, and 7.—[From the authors' summary.]

INDUSTRIAL MEDICINE

1466. **The Biological Action of Degussa Submicron Amorphous Silica Dust (Dow Corning Silica). IV. Studies on Guinea-pigs Infected with Tuberculosis**
G. W. H. SCHEPERS, A. B. DELAHANT, E. J. FEAR, and J. G. SCHMIDT. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **16**, 363–379, Nov., 1957. 4 figs., 12 refs.

It was shown by Gardner in 1934 that the inhalation of dusts containing free silica can materially influence the course of experimentally induced tuberculous infection in animals, the effect depending on whether the infection follows the exposure to dust (predisposition phase), is simultaneous with it (simultaneous phase), or precedes it (reactivation phase). The authors, working at the Saranac Laboratory, Saranac Lake, New York, have attempted to determine whether the tuberculous process in animals can be similarly stimulated or modified by their exposure to synthetic submicron amorphous silica dust produced by the Degussa process. *Mycobacterium tuberculosis* var. R1 (strain $R1R_v$) was administered to guinea-pigs in the form of an atomized mist of a suspension containing 15 to 20 bacilli in each oil-immersion field. Of the animals so infected, a control group of 48 were not exposed to dust; a group of 41 were exposed immediately to an atmosphere containing Degussa amorphous silica dust, animals being killed at 2-monthly intervals for examination (simultaneous-phase study); and of a third group of 26 animals, batches of 10, 8, and 8 were exposed to the dust 2, 4, and 6 months respectively after infection, when the process, as judged from the control group, had become dormant (reactivation-phase study). The findings were also compared with those in uninfected animals exposed to the dust in a previous investigation (*A.M.A. Arch. industr. Hlth*, 1957, **16**, 203; *Abstr. Wld Med.*, 1958, **23**, 224).

The control animals developed small subpleural nodules in the early months, with some lymphoid follicular hyperplasia and abortive tubercle formation in the lungs, but very little extrathoracic dissemination. By the end of the second year all these lesions had regressed, leaving only a few foci of cellular proliferation or irregular collagenous scars. In the simultaneous-phase group the pulmonary disturbance was appreciably enhanced and could be divided into tuberculous and pneumoconiotic reactions, the latter prevailing during the later months of the investigation. The tuberculous reaction at 2 months

was distinguished from that in the control group by a greater prevalence in the lungs of tubercles containing epithelioid and giant cells, necrosis and caseation of the lymph nodes, and some dissemination into the spleen and liver. But despite its increased intensity, the tuberculous reaction was self-limiting, reaching a stage of quiescence after about 15 months. The influence of the concomitant tuberculosis on the evolution of the pneumoconiotic reaction was decidedly unfavourable, some of the foci of reaction to the dust showing augmentation and consolidation and the severity of the lesions continuing to advance during the second year although the tuberculous infection had begun to recede. The end-result was intermediate between those found in uninfected guinea-pigs exposed to Degussa dust and to quartz dust; it was not so severe as the silicotuberculosis of infected guinea-pigs exposed to quartz dust. In the reactivation-phase group exposure to Degussa dust not only failed to reactivate a dominant tuberculous reaction, but actually tended to suppress it. The effect of previous infection on the pneumoconiotic reaction of this group was an initial slight augmentation followed by inhibition.

It is concluded that dusts containing free silica, whether crystalline or amorphous, can cause some stimulation of tuberculous infection merely by their presence in the lung tissue, and not necessarily only as a result of the formation of pneumoconiotic lesions. The question of compensation for tuberculosis in persons exposed to dust but not showing silicotic lesions cannot be answered on the evidence of these experiments alone; studies with a strain of tubercle bacillus of greater virulence is suggested as one of the necessary lines of further research.

Ethel Browning

1467. **The Biological Action of Degussa Submicron Amorphous Silica Dust (Dow Corning Silica). V. Injection Studies**

G. W. H. Schepers, A. B. Delahant, D. A. Bailey, E. L. Gockeler, and W. C. Gay. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **16**, 499–513, Dec., 1957. 9 refs.

In previous reports in this series from the Saranac Laboratory, Saranac Lake, New York, the effects on various experimental animals of the inhalation of submicron silica dust produced by the Degussa process have been described. Although such dusts are unlikely to enter the human body except by inhalation, their toxicity is much more readily studied by injection methods, which enable the relative pathogenicity of dusts of various types, particle sizes, and concentrations to be assessed rapidly and their fibrogenic action and toxicity to parenchymal cells of specific internal organs to be compared.

In the present paper investigations of the effects of intraperitoneal, intratracheal, and intravenous injection of suspensions of Degussa dust are reported. In guinea-pigs intraperitoneal injection of 200 mg. of dust in a sterilized suspension in isotonic saline caused death in 2 days from generalized peritonitis. The intratracheal injection of 12·5 mg. of the dust suspended in saline at weekly intervals into rats proved lethal to the majority, 5 out of 10 animals dying after only one or 2 doses, whereas double the dose given by the same route was fairly well tolerated by guinea-pigs. Lesions in the lungs of the rats which had received intratracheal injections consisted chiefly in focal granulomata, deposition of collagen in the alveolar walls, progressive emphysema, and damage to the bronchioles, with only limited fibrosis of the lymph nodes. In the guinea-pigs' lungs, however, there were more marked and persistent changes in the lymph nodes, less residual fibrosis and bronchiolar injury, more numerous granulomata (but in the early stages only), and a more cellular, but diminishing, reaction in the alveolar walls.

Repeated intravenous injections of 5 ml. of a 1% suspension proved highly toxic to rabbits, only 2 out of 5 animals surviving a total of 20 bi-weekly injections. The occurrence of cor pulmonale in those which died within the first 3 months confirms the finding of Antweiler that siliceous substances have a pulmonary vasospastic and vasoparalytic effect. Splenomegaly and hepatomegaly were also observed, but although atrophy of the hepatic cells occurred in the animals which died, the hepatic changes were reversible in the survivors; in the kidneys, however, progressive interstitial fibrosis developed, resulting in mechanical obstruction of the flow of urine from the convoluted tubules; this specific toxic effect on the kidneys appears to be associated with a special tissue affinity in rabbits.

These investigations reveal a sharp contrast between the collagen-inducing capacity of Degussa dust when administered by injection and its limited stimulation of collagen formation when given by inhalation. They also emphasize the greater possibility of recovery from the toxic effects of Degussa silica than from those of crystalline free silica, and the importance of studying tissue reactions in more than one species of animal. The formation of pulmonary granulomata in rabbits which received the Degussa dust by intravenous injection indicates that the route of entry of the dust into the lung is not of paramount importance so long as the dust ultimately impinges on the pulmonary tissues, whether by direct contact or following the arrest of some of the particles within the capillary bed.

Ethel Browning

1468. **Hearing Loss in Relation to Industrial Noise-exposure**

W. Grings, A. Summerfield, and A. Glorig. *Industrial Medicine and Surgery* [*Industr. Med. Surg.*] **26**, 451–458, Oct., 1957. 5 figs., 2 refs.

The authors have analysed qualitatively and quantitatively a large sample of audiograms recorded at an aircraft factory, the main aims of the study being to ascertain (1) whether they provided evidence that hearing loss is caused by exposure to noise; (2) whether it is possible to determine differences in the hearing loss occurring in different occupations; and (3) the validity of comparisons based on threshold measurements collected under such circumstances.

Graphs comparing hearing loss with duration of exposure to noise were plotted for all factory workers and also for the largest single group of workers (riveters).

After correction for age it was shown that a significantly greater loss with longer exposure appears at frequencies above 2,000 c.p.s. The mean results of audiograms from two work groups, riveters and jet flight line mechanics, showed the difference of hearing loss to be a function of job classification within this particular industry.

[The authors go to great lengths to prove what is already a recognized fact, namely, that exposure to noise in excess of a certain level, and with regard to the noise spectrum, will ultimately give rise to acoustic trauma and resultant hearing loss. The amount may vary with individual susceptibility, but provided certain criteria are observed the validity of data collected in industrial situations should not present unsurmountable difficulties.] It is essential that testing conditions should be standardized, that persons applying the test should be properly trained, that a strict clinical and otological examination be carried out before entering the employment and also at subsequent testing, and finally that a standardized and properly calibrated audiometer be employed by the testers.

Further, some standard method of recording findings should be observed, and [as the authors rightly observe] accurate information regarding the ages of the persons tested, standardized specification of the noise environment, accurate record of the man's exposure history, and the dates and times within the work cycles that the measurement was made are additional essential requirements. *E. D. Dalziel Dickson*

1469. **Ozone Toxicity Studies. III. Chronic Injury to Lungs of Animals following Exposure at a Low Level**
H. E. Stokinger, W. D. Wagner, and O. J. Dobrogorski. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **16**, 514–522, Dec., 1957. 5 figs., 6 refs.

With the object of ascertaining whether injury can be caused by exposure to a concentration of ozone approximating to that of present and possible future urban atmospheres, animals of different species (mice, hamsters, rats, guinea-pigs, and dogs) were exposed for 6 hours daily for 433 days to a concentration of ozone of 1 p.p.m. Rigorous control of the concentration was maintained by hourly determinations by the alkaline potassium iodide method. Investigations were made of the effects of such exposure on mortality, body weight, arterial oxygen saturation, and histological appearance of the lungs and respiratory tract of all the animals, and on the eyes of the dogs.

The mortality of the rats and guinea-pigs was higher than that of control animals, whereas that of the hamsters was lower; the dogs were unaffected. Loss of body weight was correlated with duration of exposure only in the case of the rats. The eyes of the dogs showed no lesions. The oxygen saturation of the arterial blood was diminished only in 4 guinea-pigs which died of pneumonia, presumably initiated by the ozone. Pathological changes in the lungs of the guinea-pigs consisted in chronic bronchitis and bronchiolitis with fibrotic changes around the terminal airways, extending into the surrounding alveolar tissue, and thickening and constriction of their walls, with consequent emphysema. These lesions were present, but were less marked, in the rats, hamsters, and mice, but the dogs showed only mild irritation of the surfaces of the trachea and bronchi.

It is suggested that " on the basis of calculations involving dimensions of the trachea, larger air passages, and ventilation rates, and assuming equal cellular susceptibility of man and dog " more ozone would reach the lower portion of the human respiratory tract than that of the dog, and that the same concentration of ozone would therefore tend to cause deeper injury. It is concluded that there are positive indications that chronic injurious effects on health can occur from this constituent of common air pollutants. *Ethel Browning*

1470. **Boron Hydride (Borane) Intoxication in Man**
H. J. Lowe and G. Freeman. *A.M.A. Archives of Industrial Health* [*A.M.A. Arch. industr. Hlth*] **16**, 523–533, Dec., 1957. 18 refs.

Of the boron hydrides or boranes, diborane, a gas, pentaborane, a volatile liquid, and decaborane, a crystalline solid, are being increasingly used as high energy fuels, and cases of accidental intoxication have already been reported. A clinical and laboratory survey has been made at the U.S. Army Chemical Center, Bethesda, Maryland, of 83 persons potentially exposed to these compounds over a period of 3 years, 13 of whom (9 exposed to pentaborane, 2 to diborane, and 2 to decaborane) were admitted to hospital; detailed descriptions of 8 of the most severely affected cases are given.

Symptoms attributable to diborane were related chiefly to the respiratory system—tightness in the chest, shortness of breath, and non-productive cough; headache, drowsiness, vertigo, chills, and fatigue or muscular weakness appeared after prolonged exposure, but were less severe than after exposure to decaborane or pentaborane, with which were associated also hiccups, tremor, and sometimes convulsions. Nausea with headache was more frequently observed with decaborane and with chronic exposure to pentaborane. An outstanding characteristic of the central nervous symptoms was their latency, signs of incoordination, tremor, and convulsions often first appearing 40 to 48 hours after exposure.

Biochemical investigations were carried out at intervals of 4 to 6 months on all the exposed persons studied and included estimations of blood non-protein and urea nitrogen levels and of serum alkaline-phosphatase activity and albumin and globulin levels, and the thymol turbidity, sulphobromophthalein, and cephalin flocculation tests. The values obtained were compared with those reported in the literature for normal populations of comparable size. Evidence was obtained of both hepatic and renal damage, even in subjects without clinical symptoms, and these investigations, the authors consider, are useful screening tests for potential excessive exposure.

Abnormal haematological findings, when present, could be readily explained as the results of infection or dehydration, except in one case in which persistent leucocytosis may have been related to borane intoxication.
Ethel Browning

Forensic Medicine and Toxicology

1471. **Myonecrosis and Myoglobinuria in Alcohol and Barbiturate Intoxication.** [In English]
H. FAHLGREN, R. HED, and C. LUNDMARK. *Acta medica Scandinavica* [*Acta med. scand.*] **158**, 405–412, Oct. 15, 1957. 6 figs., 10 refs.

From Södersjukhuset, Stockholm, 5 cases of myonecrosis in male alcoholics are reported; in one case there was concurrent barbituric acid intoxication. The clinical features included aching and tenderness of the affected muscles with considerable oedema which could be mistaken for venous thrombosis. There were 2 deaths, probably in hyperpotassaemia. In 3 of the patients myoglobin was demonstrated spectroscopically in the urine. Necrosis of the muscles was confirmed histologically in 4 cases.

The part played by alcohol and barbituric acid in the aetiology of myonecrosis is discussed.

Norval Taylor

1472. **Contribution of New Immunological Methods to the Problem of the Identification of Human Blood.** (Apport des méthodes immunologiques récentes au problème de l'identification du sang humain)
J. M. FINE. *Annales de l'Institut Pasteur* [*Ann. Inst. Pasteur*] **93**, 592–601, Nov., 1957. 1 fig., 9 refs.

The decision whether or not a stain is due to human blood is probably the most important in the whole domain of forensic medicine, so that any technique that can help towards this is to be welcomed. The author describes from the Institut Pasteur, Paris, experiments designed to compare the relative value of two techniques, (1) the inhibition of human antiglobulin, and (2) the specific precipitation in an agar-gel of human serum, with and without previous electrophoresis.

Factors affecting the specificity of the first reaction were examined, especially the inhibitory action of the serum of various animal species or of different globulins on human antiglobulin sera and the possible influence of the species of animal on the test. Three antiglobulin sera were tested against human serum and serum from the chimpanzee, cynocephalus monkey, horse, goat, ox, sheep, dog, rabbit, and guinea-pig. The chimpanzee serum gave exactly the same reactions as the human, and that of the cynocephalus monkey a partial reaction. Although this antigenic community is only of theoretical importance in temperate zones, it would be important in areas where monkeys are common. In a study of the second technique specific precipitation in agar-gel was performed, (*a*) after double diffusion, and (*b*) after immuno-electrophoresis. A series of antigens was prepared from human and animal sources, together with gamma globulin from 6 animal species, excluding monkeys. Precipitating immune sera were made from these and tested against 13 human sera and sera from 12 animal species, ranging from chimpanzees to hens. A striking finding was the almost complete identity of the human and chimpanzee sera; there was also some interaction with other animal species. Immuno-electrophoresis also showed a striking resemblance between human and chimpanzee sera, not only in regard to immunology, but also in the actual migration of the serum constituents.

The author admits that the facts he reports are mainly of theoretical importance. Of the two techniques, precipitation in an agar-gel is the more useful, but he considers that the inhibition of human antiglobulin is simpler and more specific and seems to be the best test for medico-legal work at the present time. *W. K. Dunscombe*

1473. **The Precipitin Test in Elucidating the Cause of Death**
R. J. MUELLING, R. F. SAMSON, and T. BEVEN. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **28**, 489–494, Nov., 1957. 1 fig., 1 ref.

The authors, writing from Louisiana State University School of Medicine, New Orleans, draw attention to the value of the precipitin test in elucidating the cause of death in certain circumstances. Examples of its use are given in four case histories: (1) the demonstration of cobra venom in the tissues of a girl said to have been bitten by a cobra; (2) the demonstration of a precipitin for benzylpenicillin and none for horse serum in a patient to whom these substances had been administered, and who was suspected of having died from anaphylaxis; (3) the demonstration of specific antibodies to horse serum in tissue homogenates from a negro who had died within 5 minutes of receiving the usual prophylactic dose of tetanus antitoxin; and (4) the demonstration of tetanus toxin in the tissues of a patient suspected of having died of tetanus.

Two simple [and well-known] methods for the performance of the test are outlined. The first employs a capillary tube into which the antigen and antibody solutions are drawn up by means of capillary attraction, precipitation occurring at the interface. The second, employing an agar-stabilized system, is a much more elegant method with a number of advantages over the first: antibody and antigen, dissolved in agar, are separated by a zone of neutral agar into which the two diffuse, forming on contact a relatively stable ring of precipitate.

[This is a most useful paper and should be consulted for the details by those interested. The method presents possibilities of providing proof of the cause of death in cases in which it would otherwise be largely based on speculation. The value of such conclusive proof is self-evidently important in many medico-legal cases.]

Gilbert Forbes

Radiology

1474. **Significance of Early Opacification of a Cerebral Vein as Seen in 528 Cases of Serial Carotid Angiography.** (Signification de l'opacification précoce d'une veine cérébrale d'après 528 sérioangiographies carotidiennes) J. BAUMGARTNER and E. WORINGER. *Neurochirurgie* [*Neuro-chirurgie*] **3**, 180–189, July–Sept. [received Dec.], 1957. 33 refs.

In reviewing the angiograms performed at the Hôpital Pasteur, Colmar, on a number of patients suffering from various types of malignant cerebral tumour the authors frequently noted early filling of a vein which drained either the tumour itself or the region in which the tumour was developing. Struck by this fact they have reviewed all available angiograms, totalling 528. In 22 normal cases there was no example of early filling of one vein or a system of veins, but this sign was present in all the cases of arteriovenous angioma and in almost all those of glioblastoma, neurospongioma, oligodendroglioma, and astrocytoma. However, it was present in only a small number of cases of meningioma and was always in the immediate neighbourhood of the tumour. With rare exceptions, when the early venous filling was present there was correlation with the clinical, electroencephalographic, or pneumographic findings. They point out, however, that a cerebral lesion does not necessarily show itself by the presence of this early venous filling.

The angiograms were obtained by the rapid serial method on a Schönander apparatus at the rate of one per second for the first 7 seconds and then one every 2 seconds up to the 15th second. *J. MacD. Holmes*

1475. **The Roentgenography of Mammary Abscess and Mammillary Fistula**
J. GERSHON-COHEN and H. INGLEBY. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **79**, 122–128, Jan., 1958. 5 figs., 7 refs.

The authors report, from the Albert Einstein Medical Center, Philadelphia, a radiological study of 27 cases of mammary abscess, 9 of which were puerperal and 18 non-puerperal. As suggested by Gunther (*Lancet*, 1956, **1**, 175) primary breast abscesses of both categories can be classified into superficial and intramammary; secondary infections such as retromammary abscess were purposely excluded from the present study. An acute abscess appears as an irregular mass "with flame-like extensions". Initially it may be ill defined, but as the abscess localizes sharp margins appear and the centre becomes structureless. An abscess in process of encapsulation resembles a cyst, but may sometimes be differentiated from the latter by broad tentacles emerging from its margin, while in chronic abscess the poor definition of portions of the margin may help in the differentiation.

Of the authors' cases, 6 were recurrent and 4 were complicated by mammillary fistula. In the latter cases the radiographs revealed a retracted, sometimes oedematous, nipple partly surrounded by a thickened fold of skin. Dilated lactiferous ducts could be traced to the fibromuscular pad, but the sinus tract itself could only be rendered visible by the injection of opaque medium. Differential diagnosis of mammary abscess by radiography alone may be difficult or impossible. In all cases examination of the contralateral breast is essential, since unless the two breasts are compared important lesions may be missed or certain appearances may be wrongly interpreted. It is noted that in the differential diagnosis, which is discussed at some length, the possibility of secretory disease must be considered, but this is nearly always bilateral. *John H. L. Conway-Hughes*

1476. **The Occlusal Film. An Adjunct to the Roentgen Diagnosis of Nasal Fractures**
R. J. CAPAROSA and A. R. ZAVATSKY. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **66**, 503–511, Nov., 1957. 7 figs., 1 ref.

In children and adolescents the standard lateral and antero-posterior radiographs of the nose often fail to show fractures involving the cartilaginous vault. Moreover, the lateral view does not show the lateral and mesial displacements. In most cases of this type a bite film placed in the mouth between the occlusal surfaces and exposed from vertically above will show laterally displaced fragments, except in those cases in which there is insufficient projection of the nasal bones in front of a line drawn from the frontal eminence through the incisor teeth. The authors point out the value of this method as a record in cases of litigation.

F. W. Watkyn-Thomas

1477. **Radiological Changes in the Pelvis in Mongolism in Early Infancy.** (Über röntgenologische Veränderungen am Becken bei Mongolismus im frühen Säuglingsalter)
H. J. KAUFMANN and S. PELARGONIO. *Schweizerische medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **87**, 1529–1532, Dec. 14, 1957. 6 figs., 12 refs.

This report is concerned with the possible diagnostic significance of radiological changes in the pelvic bones in newborn babies with mongolism or suspected mongolism. The *x*-ray findings consist in: (1) small acetabular angle; mean average in mongolism 13 to 15 degrees compared with the normal of 28 degrees; (2) large transverse diameter of the ilium, with flaring wings; (3) elongated tapering ischium. The measurement of the acetabular angle, the iliac angle, and the iliac index according to the method described by Caffey and Ross is outlined and the findings obtained in 14 babies (17 determinations) in the neonatal period are tabulated. The values were significantly less than the normal in a high proportion of cases (acetabular angle in 84%, iliac angle in 53%, iliac index in 87%). These results con-

firm the authors' original observations and support their thesis that these changes may be the most constant skeletal feature of mongolism. Since these findings are present in the immediate post-partum period their diagnostic value, particularly in clinically doubtful cases of mongolism, is emphasized. The possibility of transitional *x*-ray changes, with low normal angle values but a typical configuration of the pelvis, is suggested. No pathogenetic explanation of the changes is available. It is proposed to undertake the study of a larger group of babies with mongolism in order to determine the diagnostic accuracy of these observations.—[From the editorial summary.]

1478. **Combined Barium Meal and Cholecystography. Report on 600 Patients**
A. S. JOHNSTONE and M. D. SUMERLING. *Lancet* [*Lancet*] **2**, 1089–1091, Nov. 30, 1957. 8 figs., 6 refs.

A technique of combined cholecystography and barium-meal examination has been adopted in the Department of Radiodiagnosis of the University of Leeds as a means of reducing the exposure of patients to radiation and of lessening pressure on the *x*-ray department. All patients over the age of 30 referred for a barium-meal examination are given a cholecystographic medium in place of the usual preparatory laxative, while a barium meal is given as a routine (before the fatty one) to all patients referred for cholecystography. As a result, 2,000 patients have now been examined by this new technique. [The proportions of patients referred initially for each type of examination are not given, and it is not stated, for instance, how many patients gave a history of preceding jaundice and colic.]

The presence of gall-stones or a non-functioning gall-bladder was demonstrated twice as frequently in women as in men, the incidence of each rising markedly with age. Of the 960 patients in whom the barium-meal findings were normal, 12% were found to have a diseased gall-bladder, as had 7·5% of the 1,040 patients with positive barium-meal findings (including, in addition to ulcers and carcinomata, such abnormalities as postoperative conditions, duodenal diverticula, and gastritis).

Denys Jennings

1479. **Abdominal Aortography in Diseases of the Kidneys and Adrenals**
P. DAMGAARD-MØRCH, O. PETERSEN, and E. SANDØE. *Danish Medical Bulletin* [*Dan. med. Bull.*] **4**, 257–261, Dec., 1957. 4 figs., 31 refs.

At Rigshospitalet, Copenhagen, abdominal aortography was carried out on 68 patients, the contrast medium being injected by the translumbar route according to the method of Dos Santos in 3 cases and by transfemoral catheterization in the remainder. Most of the patients were suffering from kidney diseases [the angiographic appearances of these are now fairly well established], but in 2 cases an adrenal phaeochromocytoma was present; in both these cases the aortogram demonstrated the tumour, although previous radiological examination after perirenal insufflation of air had not revealed any abnormality.

Severe paresis developed in one of the cases and transient renal disturbances in 4. The authors draw attention to the serious complications which sometimes accompany abdominal aortography. They consider that the procedure should be employed only when the possibilities of all other diagnostic methods have been exhausted.

D. E. Fletcher

1480. **A Comparative Study of the Therapeutic Effects of Ultra-soft, Soft, and Semi-hard *X*-rays [on Skin Disorders].** (Indagine comparativa dell'azione terapeuticadei raggi ultramolli, molli e semiduri in roentgenterapia superficiale)
A. R. COFANO. *Giornale italiano de dermatologia* [*G. ital. Derm.*] **98**, 559–584, Sept.–Oct., 1957. 10 refs.

The author presents, from the Dermatological Clinic of the University of Naples, his experience in the treatment with *x* rays of two series of cases of various skin disorders.

In the first series 76 patients suffering from 7 different conditions were treated by Bucky therapy (long wavelength) using 10 kV. Full details of the technical factors and of dosage are given. A detailed table of the results shows that these were in many cases similar to those normally obtained with much harder rays. In 14 cases of seborrhoea given a dose of 1,000 r. repeated once or twice at 30-day intervals the results were favourable, 6 being cured, 4 improved, and 4 showing no change. In pruritus ani (8 cases) and alopecia areata (8 cases), treated with smaller doses, cure was obtained in 6 and 5 cases respectively. Of 7 cases of palpebral eczema, 5 were cured, this condition being an obvious indication for treatment with rays of low penetration.

In the second series (154 cases), involving 24 different diseases including basal-cell epithelioma, mycosis fungoides, eczema, contact dermatitis, and angioma, the effects of ultra-soft, soft, and semi-hard rays were compared by treating different areas with different wavelengths. The physical characteristics and details of dosage are given. Ultra-soft rays were generated at 10 kV., soft rays at 43 to 50 kV., and semi-hard rays at 100 kV. or more. The half-value layers are given for the three different types of radiation, and the various sites treated, fields, dosage, and results are presented in extensive tables. The comparison between ultra-soft and semi-hard rays, excluding the first series, was in favour of the former in regard to psoriatic and *x*-ray-susceptible pruritic lesions, ultra-soft rays giving the better results; there was never any activation of the psoriasis by the treatment. The doses used were well within the safety limits in every case, and long intervals between sessions allowed for assessment of progress and discovery of any possible adverse effects. In the treatment of seborrhoea, alopecia areata, psoriasis, and pruritic lesions soft rays are considered inferior to ultra-soft, but never inferior to semi-hard rays. In none of the conditions treated were semi-hard rays found to be superior to either of the two others. It is suggested that for the treatment of special sites such as the eyelids, scrotum, the vicinity of centres of ossification, and articular cartilage the non-penetrating rays open a new field.

F. Hillman

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